Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2006-11

Tebuconazole

The active ingredient tebuconazole and its associated end-use product Folicur 432F Foliar Fungicide, which contains 432 g/L tebuconazole, for the control of selected diseases caused by fungal pathogen on wheat, have been granted temporary registration the Pest Control Products Regulations.

This Regulatory Note provides a summary of data reviewed and the rationale for the regulatory decision concerning these products.

(publié aussi en français)

15 December 2006

This document is published by the Alternative Strategies and Regulatory Affairs Division, Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.pmra-arla.gc.ca
Information Service:
1-800-267-6315 or 613-736-3799
Facsimile: 613-736-3758

ISBN: 978-0-662-44672-9 (978-0-662-44673-6)
Catalogue number: H113-7/2006-11E (H113-7/2006-11E-PDF)

© Her Majesty the Queen in Right of Canada, represented by the Minister of Public Works and Government Services Canada 2006

All rights reserved. No part of this information (publication or product) may be reproduced or transmitted in any form or by any means, electronic, mechanical photocopying, recording or otherwise, or stored in a retrieval system, without prior written permission of the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5.

Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued temporary registration for the technical grade active ingredient tebuconazole and the associated end-use product Folicur 432F Foliar Fungicide for the control of selected diseases caused by fungal pathogen on wheat.

Methods for analyzing tebuconazole in environmental media are available to research and monitoring agencies upon request to the PMRA.

Bayer CropScience Inc. will be carrying out additional food residue, environmental fate and environmental toxicology as well as value studies as a condition of this temporary registration. Following the review of these information, the PMRA will publish a proposed regulatory decision document and request comments from interested parties before proceeding with a final regulatory decision.

Table of Contents

1.0 The Active Substance, Its Properties and Uses 1
  1.1 Identity 1
  1.2 Physical and Chemical Properties 1
  1.3 Details of Uses 3

2.0 Methods of Analysis 4
  2.1 Analytical Methods for Analysis of the Active Substance as Manufactured 4
  2.2 Analytical Methods for Formulation Analysis 4
  2.3 Analytical Methods for Residue Analysis 4
    2.3.1 Methods for Environmental Residue Analysis 4
    2.3.2 Multiresidue Methods for Residue Analysis 5
    2.3.3 Methods for Residue Analysis of Plants and Plant Products 5
    2.3.4 Methods for Residue Analysis of Food of Animal Origin 7

3.0 Impact on Human and Animal Health 8
  3.1 Integrated Toxicological Summary 8
  3.2 Determination of Acceptable Daily Intake (ADI) 11
  3.3 Acute Reference Dose (ARfD) 11
  3.4 Toxicological Endpoint Selection: Occupational and Bystander Risk Assessment 12
  3.5 Impact on Human and Animal Health Arising from Exposure to the Active Substance or to its Impurities 14
    3.5.1 Occupational Exposure and Risk 14
    3.5.2 Residential Exposure and Risk 16
    3.5.3 Bystander Exposure and Risk 16

4.0 Residues 17
  4.1 Residue Summary 17
    4.1.1 Nature of the Residue in Plants 17
    4.1.2 Confined Accumulation in Rotational Crops 18
    4.1.3 Field Accumulation in Rotational Crops 20
    4.1.4 Nature of the Residue in Animals 21
    4.1.5 Storage Stability Data—Plant/Animals 25
    4.1.6 Crop Field Trials 25
    4.1.7 Processed Food/Feed 26
    4.1.8 Meat/Milk/Poultry/Eggs 26
    4.1.9 Dietary Risk Assessment 27

5.0 Fate and Behaviour in the Environment 28
  5.1 Physical and Chemical Properties Relevant to the Environment 28
  5.2 Abiotic Transformation 28
  5.3 Biotransformation 28

5.4 Mobility 29
5.5 Dissipation and Accumulation under Field Conditions 29
5.6 Bioaccumulation 30
5.7 Summary of Fate and Behaviour in the Terrestrial Environment 30
5.8 Summary of Fate and Behaviour in the Aquatic Environment 31
5.9 Expected Environmental Concentrations 32
  5.9.1 Soil 32
  5.9.2 Aquatic Systems—Direct Overspray 32
  5.9.3 Drinking Water 32
  5.9.4 Vegetation and Other Food Sources 33

6.0 Effects on Non-target Species 33
6.1 Effects on Terrestrial Organisms 33
6.2 Effects on Aquatic Organisms 36
6.3 Effects on Biological Methods of Sewage Treatment 38
6.4 Risk Characterization 38
  6.4.1 Environmental Behaviour 38
  6.4.2 Terrestrial Organisms 39
  6.4.3 Aquatic Organisms 42
6.5 Outstanding Data Requirements 43
6.6 Risk Mitigation 44

7.0 Efficacy 46
7.1 Effectiveness Against Target Organisms or with Respect to the Effect Achieved 46
  7.1.1 Intended Use 46
  7.1.2 Mode of Action 46
  7.1.3 Description of Pest Problem 47
  7.1.4 Effectiveness Against Pests 50
  7.1.5 Total Spray Volume 55
7.2 Phytotoxicity to Target Plants or to Target Plant Products 55
7.3 Impact on Succeeding Crops, Adjacent Crops and on Treated Plants or Plant Products Used for Propagation 55
  7.3.1 Impact on Succeeding Crops 55
  7.3.2 Impact on Adjacent Crops 55
  7.3.3 Impact on Seed Viability 55
7.4 Economics 55
7.5 Sustainability 56
  7.5.1 Survey of Alternatives 56
  7.5.2 Compatibility With Current Management Practices Including Integrated Pest Management 57
  7.5.3 Contribution to Risk Reduction 57
  7.5.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance 57
7.6 Conclusions 58

7.6.1 Summary 58

8.0 Toxic Substances Management Policy Considerations 59

9.0 Regulatory Decision 60
9.1 Label Amendments/Recommendations 60
9.1.1 Technical Tebuconazole 60
9.1.2 Folicur 432F Foliar Fungicide 61
9.2 Additional Data Requirements 64

List of Abbreviations 67

Appendix I Toxicology 71
Table 1 Summary Table 71

Appendix II Occupational Exposure Summary 91
Table 1 Exposure Estimates and MOEs for OPEN Mix, Load and Application of Folicur 432F Foliar Fungicide to Wheat 91
Table 2 PHED Exposure Estimates and MOEs for CLOSED Mix, Load and Application of Folicur 432F Foliar Fungicide to Wheat 92
Table 3 PHED Exposure Estimates and MOEs for Mix/Load Apply of Folicur 432F Foliar Fungicide to Wheat 92
Table 4 LADD and Cancer Risk Estimates for Farmers and Custom/Aerial Applicators Handling Folicur 432F Foliar Fungicide During Open Mix/Load and Application Activities 93
Table 5 Re-Entry Exposure Estimates and MOEs for Agricultural Workers Re-Entering Wheat Fields Treated with Folicur 432F Foliar Fungicide 93
Table 6 LADD and Cancer Risk Estimates During Re-Entry Activities (i.e., scouting)* 94
Table 7 Number and Location of Additional Crop Field Trials 94
Table 8 Number and Location of Additional Crop Field Trials (25% reduction) . 94

Appendix III Residues 95
Table 1 Integrated Food Residue Chemistry Summary 95
Table 2 Overview of Metabolism Studies and Risk Assessment 111

Appendix IV Environmental Assessment 113
Table 1 Physical and Chemical Properties of the Active Ingredient Relevant to the Environment 113
Table 2 Fate and Behaviour in the Terrestrial Environment 113
Table 3 Fate and Behaviour in the Aquatic Environment 114
Table 4 Major Groundwater and Surface Water Model Inputs for Level 1 Assessment of Tebuconazole 115
Table 5 Level 1 Estimated Environmental Concentrations of Tebuconazole in Potential Drinking Water Sources 115

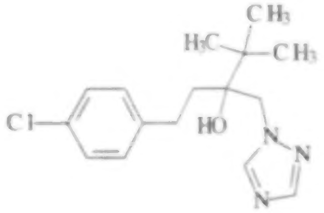
Table 6 Major Groundwater and Surface Water Model Inputs for Level 2 Assessment of Tebuconazole . . . 115
Table 7 Level 2 Estimated Environmental Concentrations of Tebuconazole in Potential Drinking Water Sources . . . 116
Table 8 Updated Level 2 Estimated Environmental Concentrations of Tebuconazole in Drinking Water (wheat 126 g a.i./ha) . . . 117
Table 9 Maximum EEC in Vegetation and Insects after a Direct Overspray . . . 118
Table 10 Maximum EEC in Diets of Birds and Mammals . . . 118
Table 11 Effects on Terrestrial Organisms . . . 119
Table 12 Effects on Aquatic Organisms . . . 121
Table 13 Environmental Risk Classification Scheme . . . 123
Table 14 Risk to Terrestrial Organisms . . . 123
Table 15 Risk to Aquatic Organisms . . . 124
Table 16 Methods for Environmental Residue Analysis . . . 125

References . . . 127

1.0 The Active Substance, Its Properties and Uses

1.1 Identity

Identification of the Technical Grade Active Ingredient

Active substance	Tebuconazole
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry	(RS)-1-p-chlorophenyl-4,4-dimethyl-3-(1*H*-1,2,4-triazol-1-ylmethyl)pentan-3-ol
2. Chemical Abstracts Service (CAS)	(±)-α-[2-(4-chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol
CAS number	107534-96-3
Molecular formula	$C_{16}H_{22}ClN_3O$
Molecular weight	307.81
Structural formula	
Nominal purity of active	95% (limits: 93–99.9%)
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade tebuconazole does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances

1.2 Physical and Chemical Properties

Technical product—Tebuconazole

Property	Result	Comment
Colour and physical state	Colourless to tan, crystalline solid	
Odour	Odourless to mildly aromatic	

Property	**Result**	**Comment**
Melting point or range	104.7°C	
Boiling point or range	Not applicable—product is a solid	
Density	1.202	
Vapour pressure at 20°C	1.3×10^{-6} Pa	Non-volatile
Henry's law constant at 20°C	1.434×10^{-10} atm•m^3/mol	Not volatile from water and moist surfaces
Ultraviolet–visible spectrum	Maximum at 220.8 nm in acetonitrile-buffer, at pH 4, 7 and 9. No absorbency at $\lambda > 300$ nm.	Low potential for phototransformation
Solubility in water (mg/L)	**Solubility** **Temperature** (°C) 21 10 32 20 52 40	Soluble in water, potential for leaching and runoff
Solubility in organic solvents at 20°C	**Solvent** **g/L** Hexane 0.08 Toluene 57 2-Propanol 99 CH_2Cl_2 > 200 Acetone > 200	
n-octanol/water partition coefficient (K_{ow})	$K_{ow} = 5000$ $\log K_{ow} = 3.70$	Potential for bioconcentration/ bioaccumulation
Dissociation constant (pK_a)	Not applicable—does not dissociate	No dissociable functionality
Stability (temperature, metal)	Compatible with glass phenolic coated steel, brass, stainless steel, aluminum, Kraft paper, polyethylene. Not compatible with plain tin-plate or plain steel. Thermal stability and no change after three years storage under ambient conditions.	

End-Use Product—Folicur 432F Foliar Fungicide

Property	Result
Colour	Off-white
Odour	Characteristic, slightly musty
Physical state	Liquid
Formulation type	Liquid suspension
Guarantee	Tebuconazole, 432g/L nominal (limits: 420–445 g/L)
Formulants	The product does not contain any United States Environmental Protection Agency (USEPA) List 1 formulants or formulants known to be TSMP Track 1 substances. One of the formulants contains an USEPA List 2 ingredient at a maximum of 0.0072%.
Container material and description	High density polyethylene; 10 L
Bulk density	1.12 g/cm^3 at 20°C
pH	9.0 (10% suspension in distilled water)
Oxidizing or reducing action	This product does not contain any strong oxidizing or reducing agents.
Storage stability	Based on the results of a one year storage stability study (under ambient conditions), the active ingredient is stable (relative a.i. loss was 0.7%).
Explodability	This product is not potentially explosive.

1.3 Details of Uses

Folicur 432F Foliar Fungicide (containing tebuconazole 432 g/L) is a systemic fungicide for use in wheat. It is recommended to suppress Fusarium head blight and control a number of foliar diseases, including rusts (leaf rust, stem rust and stripe rust), Septoria leaf blotch, tan spot and powdery mildew using ground as well as aerial equipments. The maximum application rate is 292 mL product per hectare, which is equivalent to 126 g a.i./ha. It is to be applied once per year from late vegetative stage to the end of flowering.

2.0 Methods of Analysis

2.1 Analytical Methods for Analysis of the Active Substance as Manufactured

The level of active ingredient and the impurities in the five batches plus a composite sample were determined by high performance liquid chromatography with ultraviolet detection (HPLC-UV) as well as gas chromatography with a flame inonisation detector (GC-FID), using external standard quantitation. The methods were sufficiently accurate and were determined to be suitable for the determinations. The identities of all components were confirmed by HPLC or GC retention time match with the corresponding reference standards, which were characterized by proton nuclear magnetic resonance (^{1}H-NMR), infrared (IR), ultraviolet (UV) or mass spectrometry (MS).

2.2 Analytical Methods for Formulation Analysis

The level of a.i. in the formulation was determined by GC-FID using internal standard quantitation. The method was assessed to be specific, as shown by the provided chromatograms, precise (relative standard deviation = 1.62%) and accurate (mean recovery = 99.7%) for use as an enforcement analytical method.

2.3 Analytical Methods for Residue Analysis

2.3.1 Methods for Environmental Residue Analysis

Parent Compound and Transformation Products—Soil
An extraction, clean-up as well as detection method was provided for the determination of tebuconazole in soil and turf. Samples were extracted using a Soxtec extraction unit and a 70:30 solution of methanol/water. The samples were then diluted and filtered prior to analysis. A validated high performance liquid chromatography positive ion electrospray ionization tandem mass spectrometry (HPLC/ESI-MS/MS) analytical method was developed to quantify tebuconazole in soil and turf. Liquid chromatography was performed using a Phenomenex Prodigy 5 ODS-3, 125 × 4.6 mm, 5 µm column, with a gradient mobile phase of 5 mm ammonium acetate and methanol. Quantitation was by internal standard (isotope-labelled tebuconazole) with confirmation of identity by retention time matching to a standard and by mass spectrometry. Recoveries over two levels of fortification from 0.01 to 0.10 µg/g ranged from 95.5 to 99.5% in soil and from 94.8 to 106.9% in turf. The limit of detection (LOD) for both sample types were below 0.01 µg/g. The method was assessed to be sufficiently sensitive, precise and accurate for the determination.

Parent Compound and Transformation Products—Sediment
An extraction, clean-up and detection method were provided for the determination of tebuconazole in sediment. Samples were extracted twice with ethyl acetate, and the organic layer was isolated before being evaporated to dryness. The residue was reconstituted in toluene and purified by passing through a silica gel column, concentrated and then diluted in ethyl acetate prior to analysis.

A validated analytical method, the gas chromatography using a nitrogen phosphorus detector (GC-NPD), was developed to quantify tebuconazole in sediment. Gas chromatography was performed using a 1701-CB, fused silica, 10 m × 0.25 mm, 0.1 µm column. Quantitation was by external standard (tebuconazole) with confirmation of identity by retention time matching to a standard and by mass spectrometry. Recoveries over 5 levels of fortification from 0.05 to 1.0 µg/g ranged from 75.0 to 112.5%. The LOD was below 0.05 µg/g. The method was assessed to be sufficiently sensitive, precise and accurate for the determination.

A summary of the analytical methods for detection of tebuconazole in soil, water, sediment and biota (plant matrix and animal matrix) is provided in Appendix IV, Table 16.

2.3.2 Multiresidue Methods for Residue Analysis

Tebuconazole was tested through Protocols A, C, D, E and F of the *Pesticide Analytical Manual* (PAM), volume I, United States Food and Drug Administration (USFDA). The findings indicated that recovery of tebuconazole was too low, resulting in unacceptable accuracy or interference precluding determination of the analyte. Protocol B was not tested because tebuconazole is not an acid and does not posses a phenol group. The metabolite t-butylhydroxy tebuconazole (HWG 2061; hydroxy tebuconazole) was tested through protocols A, B, C, D, E and F of the PAM, volume I (USFDA). Results indicated that either the analyte did not produce chromatographic response or problems were encountered with interferences, very low recoveries and very poor precision between duplicate analyses. The multiresidue method (MRM) testing data indicated that tebuconazole and the metabolite t-butylhydroxy tebuconazole were not recovered through Protocols A, B, C, D, E and F of the PAM, vol I. Therefore, the MRM is not applicable for enforcement purposes.

2.3.3 Methods for Residue Analysis of Plants and Plant Products

The residue of concern (ROC) for enforcement and risk assessment purposes was defined as tebuconazole. Three analytical methods for the analysis of residues of tebuconazole in plant matrices were proposed.

Method 94295 was used for data gathering purposes. The method was used in the analysis of tebuconazole residues in plant matrices (banana, peanut, barley, oat, rye, wheat and grape), soil and water. Residues were extracted from plant tissues with acetone or acetone:water, filtered, partitioned into dichloromethane and cleaned up by silica gel. Tebuconazole was determined by gas chromatography using the thermionic nitrogen-phosphorus detector; detector response was linear between 0.1–50 ng/injection. Recoveries were within a range of 80–104% for samples spiked with tebuconazole from 0.05 ppm to 0.5 or 5.0 ppm. The limit of quantitation (LOQ) was established at 0.05 ppm. It is noted that in the field accumulation in rotational crop study, the LOQ of the method was reported as 0.01 ppm for wheat grain, as validated by concurrent recovery experiments.

Method 101341 was used for data gathering and enforcement purposes. The method involved extraction of tebuconazole residues from cereal crop matrices of wheat, barley and oat samples by blending with acetone:water. After clean-up, the resulting residues were redissolved in ethyl acetate and quantitated using a gas chromatograph equipped with a thermionic (nitrogen-phosphorus) detector. The method's LOQ for tebuconazole was established at 0.01 ppm for barley and oat green forage, grain as well as straw. The LOQ for wheat was 0.01 ppm for green forage, 0.03 ppm for grain and 0.02 ppm for straw. This method was found to give good recoveries (80 ± 7% in green forage, 97 ± 5% in grain and 97 ± 7% in straw). The standard deviations measured with respect to recoveries following spiking at the LOQ did appear to be indicative of the method having good repeatability. Good linearity (correlation coefficient, $r = 0.9996$) was observed in the range of 0.025 to 2.5 µg/mL for tebuconazole. Representative chromatograms of control matrices showed little interferences in the area of elution. The peaks were well defined and well resolved from co-extractives.

The independent laboratory validation did validate the petitioner's method for analysis of the residues of tebuconazole in the various crop matrices (peanut shells, soapstock, hay, nutmeat and oil), indicating good reproducibility.

The extraction efficiency of the analytical residue method for detecting tebuconazole in crops was evaluated with matrices containing aged radioactive residues from ^{14}C tebuconazole peanut and wheat metabolism studies. The extraction efficiency of the analytical method was found to be 80 to 107%, 103%, 98% and 96%, for peanut forage, shells, nutmeat and wheat straw, respectively. The analytical method (Method 101341) has been adequately validated for the determination and enforcement of tebuconazole in plant matrices.

Method 108114 was used for data gathering purposes. The method was used in the analysis of tebuconazole residues in wheat matrices, tomato, field/sweet corn and soybean. Residues in plant matrices were extracted with acetone:water. The extracts were filtered and diluted with acetone–water. An aliquot of the diluted extract was mixed with an equal volume of internal standard of [$^{15}N_3$] tebuconazole and analyzed for tebuconazole using high pressure liquid chromatography with triple stage quadropole mass spectrometry in positive ion selected reaction monitoring (+SRM) mode. Quantitation of tebuconazole was performed using response ratios for tebuconazole (m/z 70, daughter of m/z 308) versus [$^{15}N_3$] tebuconazole internal standard (m/z 73, daughter of m/z 311).

The method's LOQ was reported as 0.01 ppm for wheat matrices, tomato, field corn forage and grain, sweet corn forage, ears and fodder as well as for soybean forage and seed; and 0.02 ppm for field corn fodder and soybean hay. Recoveries of tebuconazole residue in the plant matrices spiked with the analyte at levels ranging from 0.01 ppm to 20 ppm were 78–116% ± 1–14% (SD). These data were all within the range 70–120% ± 20% (SD) indicating that the method was acceptable in terms of accuracy and repeatability. Good linearity in detector's response (correlation coefficient, $r = 0.9992$–1) was observed in the range of 0.002 ppm to 0.4 ppm for tebuconazole in various crop matrices. Method specificity to the target analyte, tebuconazole, was ensured by using specific detector, mass spectrometry. Method 108114 is considered acceptable as a data gathering method in wheat grain, forage, hay and straw, tomato, field corn forage, grain and fodder, sweet corn forage, ears and fodder, soybean forage as well as in hay and seed.

Interference Study

The registrant provided information on the testing of 119 compounds containing nitrogen and/or phosphorus with registered tolerances in the United States in wheat, grapes, barley, peanuts or seed grasses for interference with the analysis of tebuconazole under the gas chromatographic conditions described in the enforcement method for plant (Method 101341). The results showed that these compounds did not interfere with the analysis of tebuconazole by the method.

2.3.4 Methods for Residue Analysis of Food of Animal Origin

The ROC in animal for enforcement and risk assessment purposes was defined as tebuconazole plus the metabolite, hydroxy tebuconazole. There was one analytical method proposed for the analysis of residues of tebuconazole in animal matrices.

Method 101316 was used for data gathering and enforcement purposes. Samples of bovine liver, kidney, muscle, milk as well as of poultry liver, muscle, eggs, fat, skin and eggs were extracted with methanol or hexane and methanol, filtered and the filtrate partitioned against dichloromethane/water. The aqueous extracts were hydrolyzed to solubilize conjugated HWG 2061. Extracts were purified by gel permeation chromatography followed by silica, Florisil or HPLC. Tebuconazole was determined by GLC with thermionic N/P detection while HWG 2061 was derivatized (t-butyl hydroxy group) to form the monosilyl ether prior to quantitation by GC; GC-MS (SIM) was used for the confirmation of tebuconazole and HWG 2061. The LOQ's method for tebuconazole and HWG 2061 was established at 0.1 ppm (bovine/poultry tissues and eggs) and 0.05 ppm (milk). This method was found to give satisfactory recoveries and repeatability (70–120 ± 20%) for the analysis of livestock matrices. Representative chromatograms of control livestock matrices showed no significant background interferences. The tebuconazole and HWG 2061 peaks were well defined and symmetrical. Good linearity (correlation coefficient, $r = 0.9996$), was observed in the range of 0.025 to 0.2 μg/mL for tebuconazole and HWG 2061 in tissue, milk and egg matrices.

The independent laboratory validation did support the reliability and reproducibility of the petitioner's method for the determination of residues of tebuconazole and the metabolite HWG 2061 in livestock matrices.

The efficiency of the analytical method in the extraction of bioincurred residues of tebuconazole and HWG 2061 in animal matrices was examined, using radiolabelled samples of tissues, milk and eggs from the goat as well as poultry metabolism studies. The analytical method was shown to be capable of extracting at least 97% of the total radioactivity from the bioincurred samples. Method 101316, has been adequately validated (including radiovalidation) for the determination as well as the enforcement of tebuconazole and the metabolite, hydroxy tebuconazole in animal matrices.

3.0 Impact on Human and Animal Health

3.1 Integrated Toxicological Summary

A detailed review of the toxicological database for tebuconazole was conducted. The database is complete, consisting of the full array of toxicity studies currently required for regulatory purposes. The studies were carried out in accordance with currently accepted international testing protocols and good laboratory practices. The scientific quality of the data is acceptable and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical.

Technical tebuconazole was of slight acute toxicity via the oral route of exposure, of low toxicity via the dermal route and inhalation routes of exposure. Clinical signs of neurotoxicity were observed at high doses in the acute oral studies. It was minimally irritating to the eye, non-irritating to the skin and was not a dermal sensitizer.

The formulated product, Folicur 432F Foliar Fungicide, was of low acute toxicity via the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eye and slightly irritating to the skin. Folicur 432F Foliar Fungicide was not a dermal sensitizer.

Tebuconazole, orally administered to rats as a single dose or as 14 daily doses, was absorbed from the gastrointestinal tract and was accumulated in the bile from where it was re-introduced into the intestines via the enterohepatic circulation to be eliminated via the feces. Excretion of the chemical via the urine was also significant. Excretion via respiration was very low. Very little chemical remained in the plasma for distribution to the organs and tissues. Absorption, distribution and excretion of tebuconazole were not dependent on magnitude of the dose or on multiple daily dosing. However, elimination pattern was influenced by sex; females eliminated more radioactivity via the urine and less via the feces compared to males.

Tebuconazole was completely metabolized by the rat within 48–72 h to 2 alcohols and an acid. One alcohol was conjugated to give a sulfate and a glucuronide and was further converted to a "triol", while the acid was changed to a "keto" acid. Tebuconazole was also cleaved to give free triazole as a minor metabolite in the urine.

In short-term dermal studies, no systemic toxicity was noted in treated rabbits in a three-week study. The no observed adverse effect level (NOAEL) was > 250 mg/kg bw/day. In another three-week dermal toxicity study in rabbits, the no observed effect level (NOEL) was established at 1000 mg/kg bw/day (the only dose tested), without any systemic toxicity.

In a 3-week inhalation study, a NOAEL of 0.1558 mg/L/day (equivalent to 42.3 mg/kg bw/day) was established. Increased N-demethylase activity and piloerection was observed at this dose, but these signs were not considered adverse.

Short-term oral studies (28-day and 90-day) on mice and rats indicated that the liver was the organ mainly affected. Increases in liver weight, enzyme activities (alkaline phosphatase, aminotransferases, – and O-demethylase, cytochrome P450), plasma triglyceride concentration and histopathological effects (lipid accumulation) were observed. These effects were more pronounced in females. The adrenals were affected in both studies as indicated by vacuole formation and enlarged cells. The NOAELs were 30 mg/kg bw/day and 7.5 mg/kg bw/day for the 28- and 90-day studies in rats, respectively.

In both the 13-week and 1-year dietary studies in dogs, tebuconazole had some effects on the lens of the eyes (cataracts and degeneration of the lens). The liver, spleen and adrenals were also affected as indicated by high amounts of ferric/ferrous pigments (hemosiderin) in the liver and spleen (an adverse effect) as well as vacuole formation in the adrenals. The NOAELs were set at 7.2 mg/kg bw/day, 1.05 mg/kg bw/day and 2.96 mg/kg bw/day for the 13-week and the first and second 1-year dog studies, respectively.

The carcinogenic potential of tebuconazole was studied in rats and mice. In a chronic/carcinogenicity study in rats, there was no evidence of oncogenic potential at dose levels up to and including 300 ppm (16.0 mg/kg bw/day). A NOAEL for chronic toxicity was demonstrated at 100 ppm (4.7 mg/kg bw/day) based on treatment related effects on body weight (decreased in males and females) and adrenal weight (decreased in females). Treatment related effects observed at 1000 ppm included increased ferric/ferrous content in the spleen, liver enzyme induction and cortical degeneration in the adrenal glands. At study termination, a slight non-significant increase in thyroid C-cell adenomas and carcinomas (combined) was observed in males only, however these results were in the range of historical control data provided. Tebuconazole was not considered to be carcinogenic in rats.

In chronic/carcinogenicity studies in mice, a NOAEL of 60 ppm (21.6 mg/kg bw/day) was set for chronic toxicity based on treatment related effects on the liver (periportal vacuolation, increased plasma bilirubin at 12 and 21 months at doses greater than 60 ppm). In a second chronic mouse study, a NOAEL for carcinogenicity was set at 500 ppm (84.9 mg/kg bw/day) based on the increased incidence of hepatocellular adenoma and carcinoma and combined adenoma/carcinoma in both sexes at 1500 ppm (279 mg/kg bw/day). No NOAEL for systemic toxicity was established. Tebuconazole was not genotoxic. In view of the uncertainty regarding the mode of action leading to the observed tumours in mice, it was considered appropriate to use a linear approach (low dose extrapolation) to the cancer risk assessment. Unit risks for tebuconazole, denoted by Q^{1*}, were calculated for the combined hepatocellular adenomas and carcinomas in mice.

In a two-generation reproductive study in rats, the NOAEL of 300 ppm (24.4 mg/kg bw/day) was demonstrated for maternal and reproductive toxicity based on the decreased maternal body-weight gain, decreased viability and lactation indices as well as birth weight of pups at 84.8 mg/kg bw/day. Although the no observed adverse effect level (NOAELs) and lowest observed adverse effect levels (LOAELs) were the same in parental animals and pups, certain effects in the pups (decreased viability) were considered to be more severe than those observed in the parental animals (decreased body-weight gain), suggesting evidence of increased qualitative susceptibility in offspring. In a developmental study in rats, tebuconazole was not considered to be teratogenic. The NOAEL for maternal toxicity was 23 mg/kg bw/day based on reduced body-weight gain and food consumption as well as increased liver weight at the LOAEL of 47.5 mg/kg bw/day. The NOAEL for developmental toxicity was 47.5 mg/kg bw/day based on increased resorptions, decreased number of live fetuses, reduced fetal weight as well as increased incidences of visceral (fluid in thoracic cavity) and skeletal (bipartite/dumbell-shaped thoracic vertebral centra) findings at the LOAEL of 99.8 mg/kg bw.

In oral developmental studies in mice and rabbits, qualitative increases in sensitivity of the fetus were observed based on the presence of malformations at doses where minimal maternal toxicity was observed. In mice, the maternal NOAEL was 10 mg/kg bw/day based on mild liver vacuolization and marginally increased liver enzyme activity. The maternal LOAEL was 30 mg/kg bw/day based on increased postimplantation loss. The developmental NOAEL was 10 mg/kg bw/day based on the increased incidence of severe malformations observed at the LOAEL of 30 mg/kg bw/day and above including partial acrania at 30 mg/kg bw/d and runts, exencephaly as well as cleft palate at 100 mg/kg bw/day. An increased incidence of cleft palate was also observed at a similar dose in a previous mouse developmental study, in which the livers of maternal animals were not examined. Liver effects (vacuolation) were observed in a follow-up study of maternal toxicity in mice; however, the effects were not considered adverse. Based on the effects observed in the modern study, the overall conclusion is that the malformations in mice are occurring at maternally toxic doses. In rabbits, the maternal NOAEL was set at 30 mg/kg bw/day, based on large decreases in food consumption observed at the LOAEL of 100 mg/kg bw/day. The developmental NOAEL was set at 30 mg/kg bw/day, based on increased incidence of serious multiple malformations (spina bifida, malpositioning of limbs, abdominal fissure with eventration of organs) observed at the LOAEL of 100 mg/kg bw/day.

In dermal studies, tebuconazole was not considered to be teratogenic. Pregnant mice treated with technical tebuconazole showed a NOAEL of 90 mg/kg bw/day for maternal toxicity based on histopathological and biochemical changes of the liver. A NOEL of 275 mg/kg bw/day was established for developmental toxicity based on skeletal observations. Teratogenicity was not evident at the highest dose of 780 mg/kg bw/day. A dermal study in rats showed no signs of maternal toxicity or teratogenicity at the limit dose of 1000 mg/kg bw/day.

In an acute neurotoxicity study, the LOAEL for neurotoxicity was 250 mg/kg bw based on decreased activity in motor and locomotor activity tests as well as clinical signs. There were no treatment related effects on gross pathology. The NOAEL was 100 mg/kg bw.

In a subchronic neurotoxicity study, no treatment related effects on functional observational battery or motor/locomotor activity were observed at any dose. No treatment related effects were noted during ophthalmic, gross pathologic or neuropathologic examinations. The LOAEL for systemic toxicity was 1600 ppm (107 mg/kg bw/day) based on decreased body-weight gain. The NOAEL for systemic toxicity was 400 ppm (29.2 mg/kg bw/day). The NOAEL for neurotoxicity was 1600 ppm, the highest dose tested.

In a developmental neurotoxicity study, the maternal NOAEL was set at 300 ppm (22 mg/kg bw/day) based on decreased body weight, body-weight gain and food consumption observed at the maternal LOAEL of 1000 ppm (65 mg/kg bw/day). The developmental NOAEL was set at

300 ppm (22 mg/kg bw/day) based on increased duration of gestation, decreased total number of pups born, decreased viability index, increased number of stillborn pups, decreased pup body weight, delay in eye opening and decreased brain weights observed at the developmental LOAEL of 1000 ppm (65 mg/kg bw/day). There was no evidence of neurotoxicity.

3.2 Determination of Acceptable Daily Intake (ADI)

Non-Cancer Endpoints

The recommended ADI for tebuconazole is 0.003 mg/kg bw/day. The second 1-year dog study was considered the most appropriate study to assess chronic dietary exposure because the NOAEL is the highest of the two 1-year dog studies and the dose range in the second 1-year dog study is narrower. The NOAEL was 2.96 mg/kg bw/day, based on hypertrophy in the adrenal zona fasciculata (all animals) and the presence of fatty vacuoles in the adrenal zona glomerulosa cells at the LOAEL of 4.39 mg/kg bw/day. An uncertainty factor (UF) of 1000-fold is applied, 100-fold to account for intraspecies and interspecies variability, an additional 10-fold safety factor for the protection of infants and children, based on the increased qualitative and quantitative sensitivity in the mouse and rabbit developmental studies, as indicated by teratogenicity in the fetus at dose levels that exhibited minimal maternal toxicity. This provides a margin of safety (MOS) of 1000 to the NOAEL of 3.0 mg/kg bw/day for this endpoint (neonatal toxicity).

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF}} = \frac{2.96\ \text{mg/kg bw/d}}{1000} = 0.00296 = 0.003\ \text{mg/kg bw/day}$$

MOS for Other Critical Endpoint(s)

The most appropriate NOAEL for reproductive effects is 24.4 mg/kg bw/day based on decreased maternal body-weight gain, decreased viability and lactation indices as well as birth weight of pups at the next highest dose of 84.8 mg/kg bw/day. The MOS for reproductive effects is 8133.

The most appropriate NOAEL for the specific endpoint of cataracts in dogs is 7.2 mg/kg bw/day, based on the NOAEL from the 90-day dog study. The MOS for cataracts is 2400.

Cancer Endpoints

A $Q^{1}*$ value was determined for tebuconazole due to the carcinogenic potential of this compound observed at the highest dose in the mouse 21-month chronic study. The highest $Q^{1}*$ value was selected based on incidence of hepatocellular adenomas in male mice. The value of the $Q^{1}*$ is 5.89×10^{-3} (mg/kg bw/day)$^{-1}$.

3.3 Acute Reference Dose (ARfD)

Females 13+

The recommended ARfD for tebuconazole for females 13 years of age and older is 0.03 mg/kg bw. The most appropriate study for selection of a toxicity endpoint for acute dietary exposure was the developmental toxicity study in mice, with a NOAEL of 10 mg/kg bw/day, based on the increased incidence of malformations observed at the LOAEL of 30 mg/kg bw/day including acrania. A safety factor of 300 is recommended. The standard safety factor of 100 is applied to account for intraspecies and interspecies variability, and an additional 3-fold safety factor is recommended for the protection of infants and children, based on the increased qualitative sensitivity in the rat reproduction, mouse and rabbit developmental studies, as indicated by decreased viability and teratogenicity in the fetus at dose levels that exhibited maternal toxicity.

$$\text{ArfD} = \frac{\text{NOAEL}}{\text{UF}} = \frac{10 \text{ mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw}$$

3.4 Toxicological Endpoint Selection: Occupational and Bystander Risk Assessment

Folicur 432F Foliar Fungicide will be applied once per season at a maximum application rate of 126 g a.i./ha (i.e., 292 g product/ha) using ground or aerial application equipment. Exposure of farmers, custom and aerial applicators during mixing, loading and application is expected to be short-term in duration (i.e., 1–30 days). Based on the nature of the re-entry activities (e.g., scouting), postapplication exposure is expected to be intermittent when it occurs and short- to intermediate-term in duration. Exposure is predominately by the dermal route, with inhalation exposure accounting for a maximum of 5% of total exposure.

For short- and intermediate-term occupational exposures via the dermal route, the mouse dermal developmental toxicity study with a NOAEL of 275 mg/kg bw/day was considered most appropriate, based on increased ALAT activity in the liver and increased relative adrenal weights in the dams at the LOAEL of 780 mg/kg bw/day. Increased incidences of palatoschisis, bipartite sternebrae and non-ossification of the forelimb distal phalanx and supernumerary ribs were noted in the pups at the LOAEL of 780 mg/kg bw/day. A safety factor of 300 is recommended. The standard safety factor of 100 is applied to account for intraspecies and interspecies variability, and although no fetal sensitivity was noted in the mouse dermal developmental study, an additional 3-fold uncertainty factor to account for the severity of endpoints noted in the mouse and rabbit oral developmental studies in the presence of maternal toxicity. Therefore, the target MOE for these scenarios is 300.

The mouse dermal developmental NOAEL was selected over the two short-term dermal studies in rabbits (NOAELs of > 250 mg/kg bw/day and equal to 1000 mg/kg bw/day) because no developmental endpoints were examined in these short term rat or rabbit studies.

For short- and intermediate-term occupational exposures via the inhalation route, the mouse oral developmental study with a NOAEL of 10 mg/kg bw/day was considered most appropriate, based on the incidence of malformations observed at the LOAEL of 30 mg/kg bw/day including partial acrania. A safety factor of 300 is recommended. The standard safety factor of 100 is applied to account for intraspecies and interspecies variability, and an additional 3-fold uncertainty factor to account for the severity of endpoints noted in the mouse and rabbit developmental studies in the presence of maternal toxicity. Therefore, the target MOE for these scenarios is 300.

The mouse oral developmental NOAEL was selected over the short-term inhalation study in rats (NOAEL = 0.1558 mg/L/day approximately equivalent to 42.3 mg/kg bw/day) because no developmental endpoints were examined in this study.

For the cancer risk assessment, in view of the uncertainty regarding the mode of action leading to the observed tumor response, it was considered appropriate to use a quantitative approach. A Q^{1*} value was determined for tebuconazole due to the carcinogenic potential of this compound observed at the highest dose in the mouse 21-month chronic study. The highest Q^{1*} (representing the upper 95% confidence limit on the slope of the dose-response curve in the low-dose region) value was selected based on incidence of hepatocellular adenomas in male mice. The value of the Q^{1*} is 5.89×10^{-3} (mg/kg bw/day)$^{-1}$. This value was used for the cancer risk assessment for mixer/loader/applicator as well as for postapplication scenarios.

Dermal Absorption

Dermal absorption of [^{14}C]-HWG 1608 (tebuconazole) was investigated in an in vivo rat study. Male rats were treated dermally with technical grade HWG 1608 at 4 dose levels: 0.604 µg/cm², 5.86 µg/cm², 52.4 µg/cm², and 547 µg/cm². Sacrifices were made at 0.5 h, 1 h, 2 h, 4 h, 8 h, and 24 h after application of the dose. The application site was washed just prior to sacrifice. The mean total recovery of radioactivity among the treated groups ranged from 91% to 105%.

The total radioactivity absorbed includes the amount directly absorbed, plus the amount retained in the skin at the application site (potentially available for absorption). Of the total percent radioactivity absorbed, the majority was from the skin test site. The 8-hour low dose absorption value of 51.8% was considered most appropriate for the proposed use scenario. The value of 51.8% is based on the sum of the mean percent directly absorbed plus the mean percent retained in the skin.

Dermal absorption of [^{14}C]Folicur EW 2509 was also investigated in an in vivo primate (Rhesus monkey) study. The PMRA has conducted a preliminary review of this study. Male Rhesus monkeys were treated dermally with an aqueous solution of ^{14}C- Folicur EW 250 at a dose rate of 5.48 µg/cm². The animals were restrained for eight hours, after which the application site was rinsed. The animals were then placed in metabolism cages and urine, feces as well as cage debris were collected at 8–12 hour and 12–24 hours postdose and at 24-hour intervals up to 120 hours postdose. Mean total of excreted radioactivity was 11.51%, and total recovery from the application area was 76.86%. Based on a preliminary review, a dermal absorption value of 25% was derived, based on the sum of excreted radioactivity and radioactivity not recovered.

Based on the above two studies, a dermal absorption value of 25% was selected for use in the exposure assessment.

3.5 Impact on Human and Animal Health Arising from Exposure to the Active Substance or to its Impurities

3.5.1 Occupational Exposure and Risk

3.5.1.1 Mixer/Loader/Applicator Non-Cancer Endpoints

Folicur 432F Foliar Fungicide would be applied using ground or aerial application equipment. Exposures from mixing, loading and applying the product to wheat by farmers and custom applicators were estimated using the Pesticide Handlers Exposure Database (PHED) version 1.1. The PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. The PHED subsets compare well to the proposed formulation and use pattern; therefore, they are acceptable as surrogate data for estimating exposure to tebuconazole. To estimate exposure for each use scenario, appropriate subsets of A and B were created from the following PHED files:

- liquid open mixer/loader;
- liquid closed mixer/loader;
- groundboom open cab applicator;
- groundboom closed cab applicator; and
- aerial application—rotary and fixed wing aircraft.

The PHED estimates meet the criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. The primary route of exposure was dermal, with inhalation accounting for a maximum of 5.0% of total exposure.

The exposure estimates and MOEs for farmers, custom applicators as well as aerial applicators mixing/loading/applying Folicur 432F Foliar Fungicide while wearing coveralls over a single layer (long-sleeved shirt and long pants) and gloves are summarized in Appendix II, Table 1 (open mix/load) and Appendix II, Table 2 (closed mix/load). Appendix II, Table 3 summarizes the daily exposures and MOEs based on the application and clothing scenarios anticipated to be practised in the field.

The MOE for farmers who handle the 9.5 L jugs (i.e., open mix/load) and who apply the product using open cab equipment is acceptable provided that a maximum of 100 hectares are treated per day. Operators must wear cotton/polyester coveralls over a long-sleeved shirt, long pants and chemical resistant gloves during mixing, loading, application, clean-up and repair activities. Applicators who spray more than 100 hectares per day must use closed transfer equipment (i.e., totes) during mix/load activities. All workers must wear cotton/polyester coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves during mixing, loading, application, clean-up and repair activities. Coveralls are not required during application within closed cabs or cockpits.

Flagger Exposure
An exposure estimate and risk assessment for flaggers was not conducted as it is standard practice for aerial applicators to use global positioning systems during aerial application. Although human flaggers may still be used occasionally, exposure to human flaggers is expected to be less than that for mixer/loaders.

3.5.1.2 Mixer/Loader/Applicator Cancer Endpoint

To calculate the potential lifetime exposure of agricultural workers handling Folicur 432F Foliar Fungicide, mixer/loader/applicator exposures are amortized over an individual's lifetime. This is expressed as the lifetime average daily dose (LADD) and takes into account multiple exposure scenarios as well as the frequency of exposure scenarios throughout the individual's lifetime. The LADD was based on the following assumptions:

- farmers could mix/load/apply Folicur 432F Foliar Fungicide for 2 days/season;
- custom applicators could mix/load/apply Folicur 432F Foliar Fungicide for up to 30 days; and
- for aerial application, mixer/loaders and pilots could handle Folicur 432F Foliar Fungicide for up to 15 days/year.

Farmers, custom applicators and aerial applicators could potentially have a working tenure of 40 years and life expectancy is assumed to be 75 years. The cancer risk was estimated by multiplying the LADD by the Q^1*. The Q^1* value of 5.89×10^{-3} $(mg/kg\ bw/day)^{-1}$ is based on mouse liver tumors including the combined incidences for liver adenomas and carcinomas in both sexes. The LADD and cancer risk estimates for agricultural workers exposed to Folicur 432F Foliar Fungicide as a result of mixing/loading/application and postapplication activities to wheat are summarized in Appendix II, Table 4.

The cancer risk for applicators (i.e., farmers, custom and aerial applicators) are considered acceptable.

3.5.1.3 Postapplication Non-Cancer Exposure and Risk

A dislodgeable foliar residue (DFR) study was not submitted. Therefore, exposures during postapplication activities were based on the following assumptions:

- farmers are involved in re-entry activities (i.e., scouting) for wheat for up to 12 days/year, while custom applicators or professional scouts are involved in re-entry activities for up to 30 days/year (short-term); and
- the DFRs are assumed to be 20% at time zero (when spray has dried) and residues dissipate at a rate of 10% per day.

For wheat, a range of re-entry activities take place at difference stages of cultivation. Pest scouting was identified as a frequent activity involving foliar contact. In general, scouting is not performed by farmers or custom applicators, rather it is typically conducted by agrologists or professional scouts. Re-entry exposure estimates were calculated using the following inputs: an application rate of 1.26 µg a.i./cm², a transfer coefficient of 1500 cm²/hr for scouting wheat, a dermal absorption value of 25%, 4 hours exposure per day and a 70 kg bw. Based on the nature of the re-entry activities and the proposed application rates, re-entry exposure is expected to be short- to intermediate-term on an intermittent basis. The exposure estimates, daily dose and MOEs for farmers and professional scouts re-entering treated fields are summarized in Appendix II, Table 5.

The target MOE of 1000 is achieved with a re-entry interval of 6 days.

Cancer Risk Evaluation
To calculate the potential lifetime exposure of agricultural workers exposed to tebuconazole residues as a consequence of postapplication activities (i.e., scouting), exposures are amortized over an individual's lifetime. This is expressed as the LADD and takes into account the frequency of exposure throughout the individual's lifetime.

The LADD for professional scouts and agrologists is based on re-entering treated fields for 30 days/season. The LADD for farmers is based on re-entering treated fields for 12 days/season. Since farmers may conduct both mixer/loader/applicator and re-entry activities (total of 14 days/season), these exposures were aggregated to estimate total cancer risk. Re-entry workers could potentially have a working tenure of 40 years, and life expectancy is assumed to be 75 years.

The cancer risk for re-entry workers (i.e., professional scouts and agronomists) and for farmers conducting mix/load/apply as well as re-entry activities are considered acceptable.

3.5.2 Residential Exposure and Risk

3.5.2.1 Handler Exposure and Risk

There are no domestic products; therefore, a residential handler assessment was not required.

3.5.2.2 Postapplication Exposure and Risk

There is no postapplication exposure associated with the use of this product; therefore, a residential postapplication assessment was not required.

3.5.3 Bystander Exposure and Risk

For the proposed agricultural use scenario, bystander exposure and risk during and after application were considered minimal compared to mixer/loader/applicator scenarios; therefore, they were not quantified.

4.0 Residues

4.1 Residue Summary

4.1.1 Nature of the Residue in Plants

In the wheat metabolism study carried out with a single foliar application of [triazole-UL-^{14}C] tebuconazole at the boot stage of growth at a rate of 500 g a.i./ha/season, tebuconazole was identified in wheat chaff, straw and forage with 56% total radioactive residue (TRR), 90% TRR and 99% TRR, respectively, indicating little or no metabolism of tebuconazole occurring in the foliage of the plant. In contrast, wheat grain contained small amount of tebuconazole (6% TRR) indicating extensive metabolism of the parent occurred. The major metabolic products in the grain, harvested 50 days after the application of tebuconazole, were triazolylalanine (80% TRR) and triazolylacetic acid (13% TRR) demonstrating that cleavage of the parent molecule occurred resulting in the liberation of the triazole ring with further modification to form triazolylalanine and triazolylacetic acid. The proposed metabolic pathway of tebuconazole in wheat is depicted in Figure 4.1.1.1. Triazolylalanine was the major residue (80% TRR) found in the grain. It should be noted that triazolylalanine, which is derived from the triazole ring resulting from cleavage of the parent molecule, is not specific to tebuconazole and is common to fungicides belonging to the triazole family.

Tebuconazole-phenyl ring-UL-^{14}C was applied as a foliar spray to vines and grapes 28 days before harvest at a rate of 280 g a.i./ha. The predominant residue in the surface rinse and the marc was tebuconazole; TRR levels were 85 to 99% and 8 to 11%, respectively for surface rinse and marc.

Tebuconazole radiolabelled in the phenyl-ring was applied as 7 foliar sprays to peanut plants at a rate of 204 g a.i./ha 6, 9, 11, 13, 15, 17 and 19 weeks after planting for a total rate of 1.4 kg a.i./ha. Tebuconazole was the predominant residue in peanut kernel, foliage and shell, with 19% TRR, 70% TRR and 58% TRR, respectively.

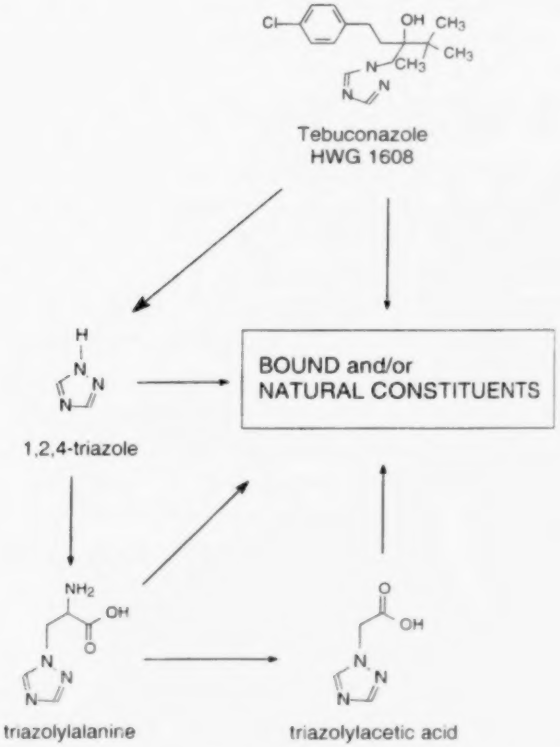
Tebuconazole radiolabelled in the triazole-ring was applied as 3 foliar applications to peanut plants 49 days before harvest at a rate of 250 g a.i./ha for a total rate of 750 g a.i./ha. In peanut kernel, predominant residues were triazolylalanine, 46% TRR; triazolyllactic acid, 9% TRR; and triazole, 9% TRR. In foliage, predominant residues were tebuconazole, 58% TRR; and HWG 2061 (hydroxy tebuconazole), 15% TRR. In peanut shell, the predominant residue was tebuconazole, 16% TRR.

Even though a wheat metabolism study using the tebuconazole compound radiolabelled in the phenyl-ring was required, it was not carried out. However, there are additional metabolism information on grapes (phenyl-ring label study) and peanuts (both phenyl-ring and triazole-ring label studies), and it appears that the metabolite profile is the same for the phenyl and triazole labelled compound.

The current petition is on wheat only; therefore, for the purposes of this submission, sufficient information to define the ROC on wheat is available. Due to a lack of contemporary information, the metabolism of tebuconazole in diverse crops is not fully understood.

Based on these data, the ROC in wheat may be defined as tebuconazole.

Figure 4.1.1.1 Proposed Metabolic Pathway of Tebuconazole in Wheat



4.1.2 Confined Accumulation in Rotational Crops

Study No. 1

Tebuconazole, radiolabelled in the triazole-ring, was applied as a foliar spray at a rate of 500 g a.i./ha to the target crop (wheat). The wheat was harvested and the sandy loam soil retreated with the same dose. The total treatment rate was 1000 g a.i./ha, which was 8 times the maximum proposed seasonal application rate. At 29, 122 and 273 days after the last treatment, kale, red table beet and spring wheat were planted as rotational crops. TRRs in the rotational crops were found to range from 0.2 ppm to 35.4 ppm, and the maximum residues occurred at the 122-day plantback interval.

Results demonstrated that tebuconazole was extensively metabolized in the rotational crops into 3 major products: triazolylalanine (31–80% TRR), triazolylacetic acid (21–54% TRR) and triazolyllactic acid (37–54% TRR). The amount of tebuconazole in the rotational crops was small, ranging from 1.7 to 15% TRR. Triazolylalanine was the major component in the wheat grain averaging 60.9% TRR, beet roots 55.0% TRR and kale 73.4% TRR. Triazolyllactic acid was the major metabolite present in wheat straw with about 35.7% TRR and beet tops 34.6% TRR. Triazolylacetic acid accounted for 50.8% TRR of the radioactivity in the immature wheat.

Metabolism of tebuconazole in the three rotational crops was similar and involved cleavage of the tebuconazole molecule at the linkage of the triazole ring giving rise to three major products: triazolylalanine, triazolyllactic acid and triazolylacetic acid. The metabolic pathway was also similar to that observed in the primary crop, wheat.

Study No. 2
Tebuconazole, radiolabelled in the phenyl-ring, was applied once and incorporated into sandy loam soil at a rate of 560 g a.i./ha (4.4 times the maximum proposed seasonal application rate). At 30, 136 and 273 days post-treatment, kale, red table beets and spring wheat were planted in the soil as rotational crops. Overall TRR in the rotational crops were low (except wheat straw), ranging from 0.020 ppm to 0.189 ppm. TRR in the wheat straw ranged from 0.117 ppm to 0.548 ppm. The maximum residues occurred at the 30-day plantback interval.

Tebuconazole was the predominant residue identified in kale, beet top and root as well as in wheat straw, with TRR ranging from 10.6% to 45.0%. The metabolite hydroxy tebuconazole was identified in wheat straw (5.2% TRR; 0.028 ppm) but was not detected in the edible portion of the rotational crops including wheat grain, kale, beet top and root. Immature wheat and wheat chaff contained a considerable amount of radioactivities of organosoluble nature (6.2–43.6% TRR). In contrast, wheat grain contained very low amount of residues of organosoluble nature (4.2% TRR; 0.002 ppm). In wheat grain, the majority of radioactivity (65% TRR) were found to reside in the aqueous fraction. Significant amount of radioactivity of aqueous nature was also reported in all the other rotational crops (20–57% TRR). It was noted that the overall absolute amount of the residues of aqueous nature in the rotational crops, except wheat straw, was low (TRR ranging from 0.005 ppm to 0.063 ppm). Wheat straw contained the highest amount of radioactivity of aqueous nature, with 0.181 ppm. Attempt to characterize the radioactivity in the aqueous fractions, using wheat straw, was made. However, due to insufficient sample materials, the characterization process could not be completed. An additional study (Study no. 3) was carried out using wheat as the rotational crop to elucidate the nature of the residues in the aqueous fraction.

It can be concluded that tebuconazole was significantly metabolized in the rotational crops. This finding was similar to that observed in the triazole-ring label study. Tebuconazole was identified as the predominant residue in the rotational crops except wheat grain in which the majority of the radioactivity was found to reside in the aqueous fraction. Considerable amount of residues of aqueous nature was also noted in the rotational crops.

Study No. 3
This study was carried out to supplement Study no. 2 and was aimed at elucidating the nature of the residues in the aqueous extracts isolated in that study.

Tebuconazole, radiolabelled in the phenyl-ring, was applied once to sandy loam soil at a rate of 2520 g a.i./ha. At 32, 152, 272 and 363 days post-treatment, spring wheat was planted in the soil as rotational crop. However, due to crop failure (explanation unclear), the 272-day and 363-day post-treatment rotational crop samples were not analyzed. Predominant residues in wheat grain were 5 anionic polar metabolites isolated from aqueous extracts, accounting for 65% TRR. Other predominant residues included tebuconazole in immature wheat (54–62% TRR), straw (11–36% TRR) and chaff (10-54% TRR); acetylated hydroxy tebuconazole glucoside in immature wheat (0–10% TRR), straw (10–18% TRR) and chaff (0–13% TRR); and hydroxy tebuconazole glucoside B in immature wheat (0–10% TRR), straw (13–15% TRR) and chaff (11–18% TRR). The maximum residues occurred at 32-day plantback interval.

The metabolic pathway appears to proceed via hydroxylation of the parent compound with possible further conjugation. During the metabolic process, loss of chlorine, butyl and methyl groups may occur. Further degradation into smaller polar residues via cleavage at the linkage of the phenyl and triazole rings may also take place.

Conclusion

It can be concluded that tebuconazole is extensively metabolized in the rotational crops to three major products: triazolylalanine, triazolylacetic acid and triazolyllactic acid. The metabolic pathway appears to proceed via hydroxylation of the parent compound with possible further conjugation. During the metabolic process, loss of chlorine, butyl and methyl groups may occur. Further degradation into smaller polar residues via cleavage at the linkage of the phenyl and triazole rings may also take place. The free triazole molecule is further metabolized to three major products: triazolylalanine, triazolylacetic acid and triazolyllactic acid.

Soil TRR levels were determined in all three studies, and characterization of the radioactivity was carried out in studies no. 2 and no. 3. It was shown that the majority of the extracted radioactivity (close to 90%) in the soil was attributable to tebuconazole.

The magnitude of the residues in the rotational crops from all the confined crop rotation studies trigger a need for field accumulation studies.

4.1.3 Field Accumulation in Rotational Crops

Quantifiable residues were found in the confined rotational crop studies; therefore, field accumulation in rotational crop was determined at two sites. Tebuconazole was applied to sandy loam or silty clay loam soil at 1750 g a.i./ha. Rotational crops including spinach, wheat or sorghum, and turnip were planted at 30-day and 120-day post-treatment and grown to maturity. No tebuconazole residues above the LOQ, ranging from 0.01 ppm to 0.03 ppm depending on crop matrix, were detected in the rotational crops harvested from the 120-day post-treatment.

4.1.4 Nature of the Residue in Animals

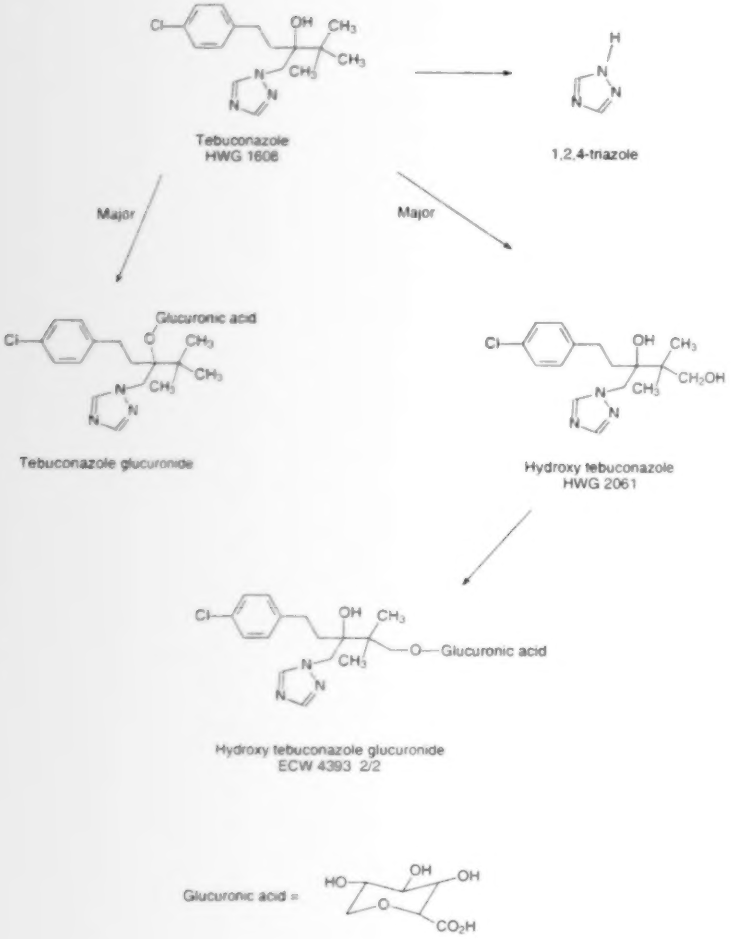
Goat

In the goat metabolism study, tebuconazole, radiolabelled in the phenyl-ring, was administered orally to a lactating goat at dose level of 15 mg/kg/day. The predominant residues were glucuronide conjugate of HWG 2061, ranging from 49 to 93% TRR in liver, kidney, muscle, fat and milk; HWG 2061, ranging from 2 to 22% TRR, in all tissues and milk; and tebuconazole, ranging from 2 to 14% TRR in liver, kidney, fat and milk.

In another goat metabolism study, tebuconazole, radiolabelled in the triazole-ring, was administered orally to 2 lactating goats (*Capra hircus*) at dose level of 3 mg/kg/day. The predominant residues in liver, kidney, muscle, fat and milk were glucuronide conjugate of HWG 2061, ranging from 54 to 77% TRR, and tebuconazole, ranging from 3 to 18% TRR. The conjugate, glucuronide tebuconazole, was observed as another predominant residues in the liver and kidney, comprising 17 to 36% TRR in these matrices. These results were consistent with those obtained in the phenyl-ring label study.

Results from the two goat metabolism studies were similar, both qualitatively and quantitatively. The metabolic pathway of tebuconazole in goat appeared to proceed either via oxidation of the parent compound to hydroxy tebuconazole with further conjugation with glucuronic acid to form hydroxy tebuconazole glucuronide (in liver, kidney, fat, muscle and milk) or conjugation of the parent compound with glucuronic acid to form tebuconazole glucuronide (in liver and kidney only). Cleavage of tebuconazole to free-form 1,2,4-triazole did not appear to be a major metabolic route since significant amount of the metabolite was not observed in the tissues although an unidentified metabolite detected in the methanol extract of milk, with very low TRR levels (0.001 ppm), was shown to have polarity similar to 1,2,4-triazole. The metabolic pathway of tebuconazole in lactating goat is depicted in Figure 4.1.4.1.

Figure 4.1.4.1 Proposed Metabolic Pathway of Tebuconazole in Goat


Tebuconazole
HWG 1606
1,2,4-triazole
Major
Major
Tebuconazole glucuronide
Hydroxy tebuconazole
HWG 2061
Hydroxy tebuconazole glucuronide
ECW 4393 2/2
Glucuronic acid =

Hen

Three hen metabolism studies were submitted. Two were carried out in 1991 and one in 2002. The two 1991 studies were carried out with tebuconazole radiolabelled in the phenyl-ring; the 2002 study, with tebuconazole radiolabelled in the triazole-ring. In the two 1991 studies, laying hens were dosed orally with [phenyl-UL-^{14}C] tebuconazole at 10 mg/kg for 3 consecutive days. At 3.5 hours (in one study) and 0.5 hours (in the other study), postdose (last dose), the hens were sacrificed. Tissues including liver, kidney, fat, skin, muscle, gizzard (in one study), heart (in one study) and eggs were analyzed for ^{14}C-residues. In the 2002 study, laying hens were dosed orally with [triazole-3,5-$^{14}C_2$] tebuconazole for three consecutive days and sacrificed 30 minutes after the last dosing. Eggs were collected daily during the dosing period, and tissues including liver, muscle and fat, were obtained at the time of sacrifice. Radioactive residues in the tissues and eggs were analyzed. Radioactive content in the excreta was measured in only one study.

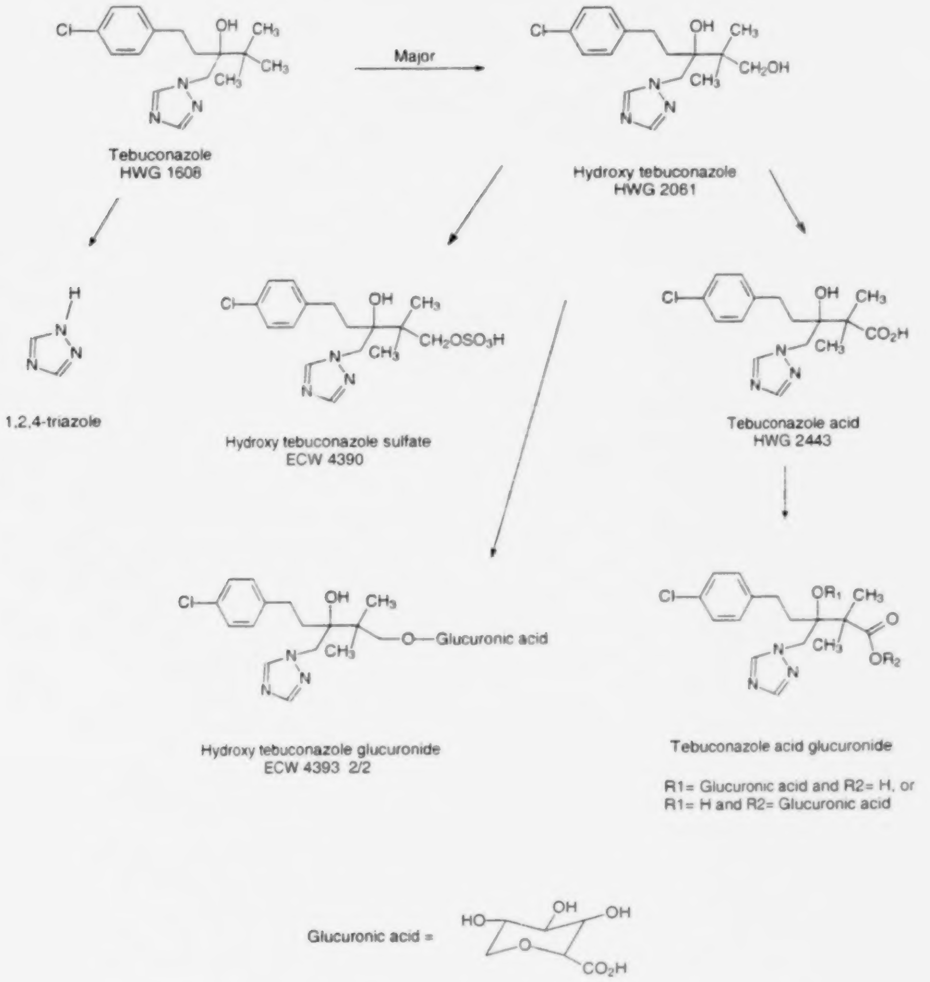
It was shown that, in the 1991 study, approximately 81% of the administered dose were recovered in the excreta, and the total radioactivity in the tissues and organs amounted to 3.75% of the administered dose. In the 2002 study, the total radioactivity recovered from all tissues and eggs accounted for 1.8% of the administered dose. It was noted that there were less tissues and organs collected for investigation in the 2002 study (kidney, heart, gizzard and skin were not collected) during the assessment.

Results from the three studies were consistent and adequately delineated the fate and disposition of tebuconazole in hen. Of the tissues analyzed in all three studies, highest TRRs were observed in liver, followed by kidney and other tissues (fat, skin, gizzard and heart); muscle and eggs contained the lowest TRRs. Tebuconazole and hydroxy tebuconazole were present in all matrices with TRRs ranging from 2 to 94% and 3 to 49%, respectively. The metabolites, hydroxy tebuconazole sulfate (ECW 4390) and tebuconazole acid (HWG 2443) were present in liver, kidney, skin, muscle and eggs with TRRs ranging from 4 to 72% and 6 to 51%, respectively. Small amount (approximately 14% TRR) of 1,2,4-triazole was observed in muscle and eggs.

Similar metabolism was shown in these studies: oxidation of tebuconazole to hydroxy tebuconazole was the major metabolic route observed. The pathway further proceeded either by conjugation of the oxidation product with sulfate or glucuronic acid forming ECW 4390 and hydroxy tebuconazole glucuronide, respectively, or by further oxidation of HWG 2061 forming HWG 2443. Further conjugation of the acid with glucuronic acid could also occur. Although 1,2,4-triazole was observed in muscle and eggs indicating that cleavage of tebuconazole occurred, this is only a minor metabolic route given the low concentrations observed (0.02 ppm). Figure 4.1.4.2 shows the proposed metabolic pathway of tebuconazole in laying hen constructed from the results of the metabolism studies conducted with hen.

The ROC in animal may be defined as tebuconazole and HWG 2061.

Figure 4.1.4.2 Proposed Metabolic Pathway of Tebuconazole in Hen


Major
Tebuconazole
HWG 1608
Hydroxy tebuconazole
HWG 2061
1,2,4-triazole
Hydroxy tebuconazole sulfate
ECW 4390
Tebuconazole acid
HWG 2443
Hydroxy tebuconazole glucuronide
ECW 4393 2/2
Tebuconazole acid glucuronide
R1= Glucuronic acid and R2= H, or
R1= H and R2= Glucuronic acid
Glucuronic acid =

4.1.5 Storage Stability Data—Plant/Animals

Plant

The data presented in the freezer storage stability study indicated that residues of tebuconazole were stable at -20°C for 24 months in wheat flour, wheat bran, peanut oil and raisin; for 30 months in peach, prune, grape, apple and cherry; and for 63 months in wheat forage, wheat grain, wheat straw and peanut nutmeat. Homogenized samples were spiked at 1 ppm with tebuconazole and analyzed after storage at the specified intervals. These data validate the frozen storage conditions and durations of wheat matrices in the crop field trial and processing studies because the maximum durations of frozen storage reported in these studies (wheat grain 39 months; wheat straw 39.6 months; wheat hay 35.7 months; wheat forage 12.6 months; wheat flour, bran, shorts and germ ~6 months; aspirated grain fractions 2 months) are all within the demonstrated periods of frozen storage of tebuconazole.

Animals

In animal matrices, residues of tebuconazole and the metabolite HWG 2061 were stable at -20°C for 12 months in milk and eggs; at -24°C for 5.5 months in bovine tissues of liver, kidney, muscle and fat; at -24°C for 5.3 months in poultry skin; and at -10°C for 6 months in poultry liver and kidney, and for 12 months in poultry muscle and fat. The actual storage durations of animal matrices reported in the cattle/poultry feeding studies (eggs and poultry tissues: 5.3 months; milk and cattle tissues: 5.5 months) are all within the demonstrated storage periods. Therefore, there is no concern with storage stability of the residues in the animal matrices.

4.1.6 Crop Field Trials

Seventy-three crop field trials on wheat were conducted with either one of the end-use products, Folicur 432F Foliar Fungicide and Folicur 3.6 F Foliar Fungicide. Out of these 73 field trials, 53 were carried out in applicable Canadian representative zones (5, 7, 7A and 14). Of these 53 field trials, there were only 4 carried out with use pattern that was representative of the proposed Canadian label (one application per season at 126 g a.i./ha with preharvest interval of 30 days). The rest (49) of the field trials were either carried out at exaggerated rates (2.5× to 3× the proposed maximum application rate) or having unacceptably long preharvest interval (PHI) of (37–97 days). Tebuconazole residues in/on wheat grain from the 4 field trials carried out with use pattern that was representative of the proposed Canadian label were all below the LOQ of the respective analytical methods (0.01 ppm or 0.05 ppm).

Of the 4 field trials meeting the Canadian requirements, i.e., carried out in Canadian representative zones with use pattern that was compatible to the proposed Canadian label, two were conducted in Zone 5 and one each in Zones 7 and 14. The Canadian requirement for wheat is 20 field trials, as stipulated in Section 9 of Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*. Therefore, there were insufficient number of field trials to satisfy the guideline requirements. A total of 16 additional crop field trials will be required. It was, however, noted that there were 6 field trials, though having unacceptably long PHI (37 to 43 days), carried out under conditions that met the proposed label use pattern and the guideline requirements in terms of geographical location. These field trials all showed the same residue profile of less than the

LOQ. Therefore, it was determined to move the proposed PHI of 30 days to 36 days to include residue data from these 6 trials. As a consequence of this change in PHI, the number of field trials meeting the guideline requirements was increased from four to ten. Additional crop field trials are still needed to satisfy the guideline requirements. Appendix II, Table 7 summarizes the number and location of the additional field trials. If the residue profile of the additional field trials remains the same, i.e., below the LOQ, a 25% reduction in the number of additional field trials can be incorporated, in accordance with Section 9 of the Regulatory Directive DIR98-02. Appendix II, Table 8 provides the number and location of the additional field trials, incorporating the 25% reduction.

As an insufficient number of crop field trials were submitted, existing residue data do not support any recommendation on the promulgation of a MRL, pending the submission and review of residue data generated from the additional crop field trials. There is an existing MRL of 0.05 ppm in Canada established for tebuconazole residues in/on wheat. The MRL was promulgated in an earlier import submission on the foliar use of tebuconazole and is harmonized with the American tolerance and Codex MRL.

There were residue decline studies in wheat grain, and results demonstrated that there was no significant decline of tebuconazole residues during the period examined. However, it was noted that the period covered was from PHI 37 to 56 days, and there were no data covering the period before and at the PHI of 36 days. Thus, there is insufficient information to determine the behaviour of tebuconazole residues before and at the PHI of 36 days. Additional residue decline data in wheat grain to cover the specified period of PHI 36 days ± 7 and 14 days will be required to fully assess the residue behaviour around the PHI of 36 days.

4.1.7 Processed Food/Feed

Tebuconazole was applied to wheat at 500 g a.i./ha/season and the wheat grain or raw agricultural commodity (RAC) was processed into flour (patented), flour (low grade), bran, shorts and middlings. A comparison of the residues in the RAC with those in each processed fraction resulted in 0.13×, 0.25×, 1×, 2.5× and 0.6× for flour (patented), flour (low grade), bran, shorts and middlings, respectively. No concentration of tebuconazole residues were noted in the edible processed fractions of flour and bran. MRLs will not need to be established to cover residues of tebuconazole in wheat flour and bran.

4.1.8 Meat/Milk/Poultry/Eggs

Lactating cattle (Holstein Fresian, *Bos taurus*) were administered 30, 90 or 300 ppm tebuconazole by bolus capsules for 28 days. The maximum theoretical dietary burden (MTDB) for cattle is 9 ppm. The expected combined residues of tebuconazole and the metabolite HWG 2061 (hydroxy tebuconazole) at 3× the MTDB were below 0.2 ppm for liver, kidney, muscle and fat; and less than 0.1 ppm for milk.

Laying hens (White Leghorn, *Gallus gallus*) were fed daily rations of feed fortified with 2, 6 or 20 ppm tebuconazole for 28 days. The MTDB for poultry is 0.13 ppm. The expected combined residues of tebuconazole and the metabolite HWG 2061 (hydroxy tebuconazole) at 15× the MTDB were less than 0.1 ppm for liver, muscle, fat, skin and eggs.

The expected combined residues of tebuconazole and the metabolite HWG 2061 in meat/meat byproducts and milk/eggs resulting from the feeding of good agricultural practices (GAP) treated crops are less than 0.2 ppm and less than 0.1 ppm, respectively. There are MRLs currently established for the combined residues of tebuconazole and the metabolite HWG 2061 in animal commodities. They are 0.2 ppm and 0.1 ppm respectively for meat/meat byproducts and milk/eggs.

4.1.9 Dietary Risk Assessment

The human health risk associated with dietary exposure resulting from the use of tebuconazole in Canada and exposure to crops imported from other countries including the United States was analyzed using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID). Estimates of chronic non-cancer risk, cancer risk and acute exposure were determined. For estimation of chronic non-cancer risk, an ADI of 0.003 mg/kg bw/day, based on a NOEL of 3.0 mg/kg bw/day from a one-year dietary toxicity study in dog and an uncertainty/safety factor of 1000 was used; for cancer risk, a Q* of 0.00589 $(mg/kg\ bw/day)^{-1}$ based on a mouse liver tumor study was incorporated; and for acute exposure for the population subgroup of female 13 years old and older, an ARfD of 0.003 mg/kg bw/day based on a NOEL of 3.0 mg/kg bw/day from a mouse developmental study and an uncertainty/safety factor of 1000 was included.

The chronic non-cancer risk for the representative population subgroups as a result of dietary exposure from all supported tebuconazole food use in Canada and imported food commodities was estimated to range from 1.1% to 4.9% of ADI. The currently proposed uses for tebuconazole encompass only agricultural use sites. Therefore, when addressing aggregate exposures, only the dietary pathways of food and drinking water were considered (the expected environmental concentration [EEC] value = 1.8 µg/L, Level 2; the EEC value was based on the proposed use rate of 126 g a.i./ha/season). Aggregate exposure from food and water, which ranged from 2.0% to 6.8% of ADI, was considered acceptable and below the level of concern; the highest exposed segment is children of 1–2 years old (6.8% of ADI).

The acute exposure for the population subgroup of female 13 years old and older, at the 95th percentile, as a result of food consumption was estimated to be 4.9% and 6.7% of ARfD for pregnant/not nursing and nursing segments, respectively. The aggregate exposure from food and water was considered acceptable and below the level of concern; 6.2% and 7.8% of the ARfD for females 13 years old and older, pregnant/not nursing, and females 13 years old and older, nursing, respectively.

The cancer risk for the total population as a result of dietary exposure from all supported tebuconazole food use in Canada and imported food commodities was estimated to be 3.01×10^{-7}, which is considered acceptable and below the level of concern. When the aggregate exposure from food and water was considered, the lifetime cancer risk for the total population was less than 1 × 10^{-6}. Although this level is below Health Canada's level of concern, it does not take into consideration potential increased susceptibility from early-life exposures to carcinogens. When potential increased susceptibility from early-life exposures is taken into consideration, the outcome of the cancer risk assessment approaches Health Canada's level of concern. As such, additional food uses will not be considered for tebuconazole in the absence of additional data to refine this assessment.

5.0 Fate and Behaviour in the Environment

For a summary, see Appendix IV, Table 2 and Table 3.

5.1 Physical and Chemical Properties Relevant to the Environment

The physical and chemical properties of tebuconazole were previously reviewed under submission numbers 1989-0604/0605.

Tebuconazole is classified as soluble in water (36 mg a.i./L). Solubility is an important factor for leaching into groundwater and runoff. Based on its vapour pressure, tebuconazole is relatively non-volatile under field conditions, and its Henry's law constant indicates that it is not volatile from water and moist surfaces. The UV visible absorption spectrum (λ_{max} 220.8 and no absorbance at $\lambda > 300$ nm) indicates that phototransformation is unlikely to occur under natural light. The log *n*-octanol–water partitioning coefficient (log K_{ow} 3.70) indicates that tebuconazole has potential to bioaccumulate/bioconcentrate. Tebuconazole has no dissociable functionality (Appendix IV, Table 1).

5.2 Abiotic Transformation

Abiotic transformation is not an important route of transformation of tebuconazole in the environment. Tebuconazole is stable to hydrolysis as well as phototransformation on soil and in water. The photolytic DT_{50} of tebuconazole in soil and water were determined to be 191 and 590 days, respectively. The vapour pressure and Henry's law constant indicate that tebuconazole is non-volatile under field conditions.

5.3 Biotransformation

Tebuconazole is not rapidly transformed in soil under aerobic condition. The DT_{50} of this compound is calculated to be 770 days (at 23°C in a sandy loam soil), indicating that tebuconazole is persistent in soil according to the classification of Goring et al. (1975). There was no significant volatile radioactivity detected at all sampling intervals. The principal soil residue was identified as parent compound. Upon termination of the experiment, 67.4% of the recovered radioactivity was identified as parent compound by thin layer chromatography (TLC) and HPLC. A significant portion of the radioactivity remained unextractable in the soil (29.1% of the applied at the end of the incubation period). Although the anaerobic soil biotransformation study did not conform to acceptable standards for the examination of biotransformation in anaerobic soil, the results of this study and the aerobic soil, aerobic and anaerobic aquatic biotransformation studies indicated that tebuconazole will persist in anaerobic environment.

Biotransformation is not an important route of transformation of tebuconazole in the aquatic environment (aerobic and anaerobic). The DT_{50} of tebuconazole in the aqueous systems (whole system) is 866 and 1386 days under anaerobic and aerobic conditions, respectively, indicating that tebuconazole is persistent according to the classification scheme of McEwen and Stephenson (1979). In the aquatic environment, tebuconazole readily partitions from water to sediments (up to 59% and 63% under aerobic and anaerobic conditions, respectively), where it persists. No major transformation products were detected; however, up to 19% of the applied was evolved as carbon dioxide over the 52 weeks in aerobic water.

5.4 Mobility

Based on laboratory studies of adsorption/desorption on a range of soils, tebuconazole has low to moderate mobility ($K_{oc\text{-}ads}$ = 462–1251) in soils according to the classification of McCall et al. (1981). The desorption K_{oc} values ($K_{oc\text{-}des}$ = 1237–2300) indicated that once adsorbed tebuconazole is less readily desorbed. There is a correlation between adsorption of tebuconazole and the soil content of clay because larger amounts of tebuconazole adsorbed to the soil having a higher content of clay.

The soil TLC (Rf values of 0.09–0.22) and aged soil column leaching studies (treated soil aged for 30 and 90 days duration) indicated that tebuconazole has a low potential for mobility in soil. Less than 1% of the radioactivity leached through the column (44.5 cm in length), and most of the recovered radioactivity was identified as tebuconazole. Other extracted radiolabelled compounds were reported to be less than 10% of the total recovered radioactivity.

Based on the vapour pressure and Henry's law constant, tebuconazole is unlikely that a significant proportion of the tebuconazole applied will volatilize from the field.

Adsorption/desorption results for triazole, identified by the applicant as a transformation product, on a range of soils showed that tiazole has very high to high mobility in soil ($K_{oc\text{-}ads}$ = 21.1–126.7) according to the classification of McCall et al. (1981). Triazole, however, was not detected as major transformation product in any submitted laboratory studies of abiotic and biotic transformation.

5.5 Dissipation and Accumulation under Field Conditions

Terrestrial field studies on the dissipation of tebuconazole in Canada that were previously reviewed (submission numbers 1989-0604, 1991-0524) had major deficiencies. Their reviewer, however, concluded that tebuconazole will be persistent in soil (DT_{50} values were in the range of 205 to 912 days), based on the weight of evidence from these studies, and that there is a potential for carryover to the subsequent growing season. This conclusion was supported by the results from field studies conducted in the United States and reviewed under previous submissions

(DT_{50}s = 81–857 days) as well as by the results from laboratory studies on biotransformation (DT_{50} = 770 d in aerobic soil).

Currently, the applicant is conducting a multiyear field study with anticipated completion in December 2004. A full assessment of the subject product will be conducted after the registrant submits this study.

5.6 Bioaccumulation

The log K_{ow} of tebuconazole is 3.70, which indicates a potential for bioconcentration/ bioaccumulation. Tebuconazole and its metabolites, however, are not expected to bioaccumulate in terrestrial or aquatic organisms, based on lack of bioaccumulation and rapid depuration of tebuconazole in earthworm and bluegill sunfish (the bioaccumulation studies in earthworm and bluegill sunfish were previously reviewed under submission numbers 1989-0604/0605). The bioaccumulation factors (BAFs) for earthworm, the edible, viscera and whole fish were reported to be 1.35, 13, 150 and 78, respectively. The major metabolite identified in bluegill sunfish was a glucuronic acid conjugate of t-butyl hydroxy tebuconazole representing 63.1% and 58.6% on days 28 and 35 in the viscera. The DT_{50} for depuration of the accumulated radiolabel in earthworm and bluegill sunfish ranged from one to three days. These studies indicate that tebuconazole is readily accumulated in earthworm and bluegill sunfish and is rapidly depurated; therefore, it is unlikely to bioaccumulate.

5.7 Summary of Fate and Behaviour in the Terrestrial Environment

Abiotic transformation is not an important route of transformation of tebuconazole in the environment. Tebuconazole is stable to hydrolysis and photolysis on soil and in water. The photolytic DT_{50} of tebuconazole in soil and water were determined to be 191 and 590 days, respectively. The vapour pressure and Henry's law constant indicate that tebuconazole is non-volatile under field conditions.

Tebuconazole is classified as persistent in both the terrestrial and aquatic environment. The DT_{50} of this compound is estimated to be 770 days in aerobic soil. An acceptable anaerobic soil biotransformation study was not available. However, the results of an unacceptable study and the aerobic soil, aerobic and anaerobic aquatic biotransformation studies indicated that tebuconazole will persist in anaerobic environment. The DT_{50} of tebuconazole in the aqueous systems (whole system) is 866 and 1386 days under anaerobic and aerobic conditions, respectively. In the aquatic environment, tebuconazole readily partitions from water to sediments (up to 59% and 63% under aerobic and anaerobic conditions, respectively), where it persists.

Tebuconazole shows low to moderate mobility in environmental compartments. The adsorption/desorption studies indicate that tebuconazole has low to moderate mobility ($K_{oc\text{-}ads}$ = 462–1251) in soils according to the classification of McCall et al. (1981). Once adsorbed, the desorption process will be slower than the adsorption process as indicated by the larger K_{oc} values ($K_{oc\text{-}des}$ = 1237–2300). There is a correlation between adsorption of tebuconazole and the soil content of clay because larger amounts of tebuconazole adsorbed to the soil having a higher content of clay.

The soil TLC (Rf values of 0.09–0.22) and aged soil column leaching studies indicated that tebuconazole has a low potential for mobility in soil. Less than 1% of the radioactivity leached through the column (44.5 cm in length), and most of the recovered radioactivity was identified as tebuconazole and found in the 0 to 24 cm segment. The vapour pressure and Henry's law constant indicate that tebuconazole is not likely to volatilize under field conditions.

An acceptable Canadian field dissipation study was not submitted at this time. Based on the weight of evidence from the unacceptable field dissipation studies (DT_{50}s = 205–912 days) that were submitted under submission numbers 1989-0604 and 1991-0524, the results from field studies conducted in the United States (DT_{50}s = 81–857 days), and the results from laboratory studies on biotransformation (DT_{50} in soil of 770 days), it is concluded that tebuconazole will be persistent and there is a potential for carryover to the subsequent growing season. Currently, the applicant is conducting a multiyear field study with anticipated completion in December 2004. A full assessment of the subject product will be conducted after the registrant submits this study.

Tebuconazole and its metabolites are not expected to bioaccumulate in terrestrial or aquatic organisms.

Adsorption/desorption results for triazole, identified by the applicant as a major transformation product, on a range of soils showed that tiazole has very high to high mobility in soil ($K_{oc\text{-}ads}$ = 21.1–126.7) according to the classification of McCall et al. (1981). Triazole, however, was not detected as major transformation product in any of the submitted abiotic and biotic laboratory studies.

5.8 Summary of Fate and Behaviour in the Aquatic Environment

The proposed use of Folicur 432F Foliar Fungicide on wheat could result in the entry of tebuconazole into aquatic environments through runoff and spray drift. Dissipation of tebuconazole is not likely to be affected by abiotic transformation in the aquatic environment as tebuconazole is soluble and is stable to hydrolysis and phototransformation in water (phototransformation DT_{50} = 590 d).

Biotransformation is not an important route of transformation of tebuconazole in the aquatic environment. The DT_{50} of tebuconazole in the aqueous systems (whole system) is 866 and 1386 days under anaerobic and aerobic conditions, respectively, indicating that tebuconazole is persistent according to the classification scheme of McEwen and Stephenson (1979). In the aquatic environment, tebuconazole readily partitions from water to sediments (up to 59% and 63% under aerobic and anaerobic conditions, respectively), where it persists. No major transformation products were detected; however, up to 19% of the applied was evolved as carbon dioxide over the 52 weeks in aerobic water. Tebuconazole is unlikely to bioaccumulate in aquatic organisms.

5.9 Expected Environmental Concentrations

5.9.1 Soil

The EEC of tebuconazole in soil was calculated by the reviewer to be 0.056 mg a.i./kg dry soil immediately after application, assuming a standardized soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm (equal dilution of the pesticide in 15 cm depth, and lack of dissipation), and a scenario in which the maximum Canadian label rate of 126 g a.i./ha is applied once to bare soil.

5.9.2 Aquatic Systems—Direct Overspray

The maximum seasonal application rate is used to calculate the EEC of tebuconazole from direct overspray in surface waters at 30 cm water depth (based on the assumption of equal dilution of the pesticide in 30 cm depth). The EEC of tebuconazole in water after a single application at 126 g a.i./ha is calculated to be 0.042 mg a.i./L. Laboratory studies on solubility, hydrolysis, photolysis and biotransformation in aquatic systems indicated that tebuconazole is persistent in the aqueous environment.

5.9.3 Drinking Water

Expected environmental concentrations of tebuconazole in potential drinking water sources (groundwater and surface water) were estimated using computer simulation models.
The PMRA uses these values in its dietary risk assessment.

Surface Water EECs
EECs of tebuconazole in surface water were calculated using the Pesticide Root Zone Model and the Exposure Analysis Modeling System (PRZM/EXAMS), which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in two types of vulnerable drinking water sources, a small reservoir and a prairie dugout.

Groundwater EEC
EECs of tebuconazole in groundwater were calculated using the Leaching Estimation and Chemistry Model (LEACHM), which simulates leaching through a layered soil profile over a multiyear period. The concentrations calculated by the model are estimates of the flux, or movement, of pesticide into shallow groundwater (2 or 5 m deep) with time.

A Level 1 drinking water assessment was first conducted for tebuconazole, using conservative assumptions with respect to environmental fate, application rate and timing as well as geographic scenario. The scenario producing the maximum concentration (as defined by the 90th percentile), which was selected as providing a conservative estimate of potential exposure. Appendix IV, Table 4 lists the application information and main environmental fate characteristics used in the models. Appendix IV, Table 5 provides the EECs calculated in the Level 1 drinking water assessment. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate.

A Level 2 drinking water assessment was also conducted, using refined (less conservative) values for environmental fate parameters, and representative geographic scenarios based on the use pattern of tebuconazole. Appendix IV, Table 6 lists the application information and main environmental fate characteristics used in the models. Appendix IV, Table 7 provides the EECs calculated in the Level 2 drinking water assessment.

A further refinement of the Level 2 drinking water assessment was conducted by altering applications based on crop rotations. Three additional crop rotation application schedules were tested: two out of three years, every other year, and every third year. Additional geographic scenarios were also identified based on use information. Appendix IV, Table 8 provides the EECs calculated after further refinement of the Level 2.

5.9.4 Vegetation and Other Food Sources

The EECs of tebuconazole on wildlife food sources are based on the maximum application rate of 126 g a.i./ha. A direct overspray scenario, using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994) for use in ecological risk assessment (Urban and Cook 1986), was used. The estimated EEC values of tebuconazole in vegetation and insects are provided in Appendix IV, Table 9. Based on these values, the EECs in the diet of representative non-target species are 22.06 (bobwhite quail), 4.26 (mallard duck), 63.57 (rat), 63.18 (mouse) and 95.05 mg a.i./kg dry weight diet (rabbit) (Appendix IV, Table 10).

6.0 Effects on Non-target Species

6.1 Effects on Terrestrial Organisms

Technical tebuconazole showed no toxicity to earthworms in an acute study. The lethal concentration 50% (LC_{50}) and the no observed effect concentration (NOEC) (mortality, weight loss) were reported as 1381 and 178 mg a.i./kg soil, respectively.

Tebuconazole is categorized as relatively non-toxic (contact lethal dose 50% [LD_{50}] 176 μg a.i./bee) to worker honeybees in accordance with Atkins et al. (1981) (contact LD_{50} > 10.99 μg a.i./bee). In the oral toxicity study, no deaths were reported for the bees exposed to 0.6 μg a.i./bee (the highest concentration tested).

Only one avian acute oral toxicity study was submitted and reviewed under previous submissions (1989-0604 and 1991-0524). Technical tebuconazole is categorized as slightly toxic to bobwhite quail (LD_{50} > 1200 and 1555 mg a.i./kg, male and female, respectively) on an acute oral basis in accordance with the USEPA's descriptive categorization (1985a). The NOEC was 432 mg/kg bw, based on decreased in body weight. Tebuconazole is categorized as practically non-toxic to slightly toxic to birds (LC_{50} > 5000 and > 4816 mg a.i./kg diet for bobwhite and mallard, respectively) on a short-term dietary basis in accordance with the USEPA's descriptive categorization. The NOECs were < 325 and < 4816 mg a.i./kg diet for bobwhite and mallard, respectively (1985b), based on reduced body weight. In a study investigating the reproductive effects of tebuconazole to bobwhite quail, no major effects on reproduction attributable to the test material were detected. There were no overt signs of toxicity on the parent birds, except a nervous disorder affecting the carriage of the head and effects in general coordination in one female bird in each of the 4.96 and 18.4 mg/kg (measured concentrations) groups, and one male in the 73.5 mg/kg group. The PMRA reviewer of the avian acute oral toxicity study determined the NOEC to be 18.5 mg a.i./kg, based on this disorder. It is not clear from this review why 18.5 mg a.i./kg was considered as the endpoint when a similar effect was also observed in the lowest concentration (4.96 mg a.i./kg) tested.

In a reproduction study on mallard duck, the NOEC was reported as 75.8 mg/kg (the highest measured concentration tested). No mortalities and no overt abnormal clinical signs were observed. There were no statistically significant effects on mean feed consumption or mean body weight of the birds in the treatment groups, and no significant effects on the reproductive parameters were observed.

Studies investigating the reproductive effects of technical tebuconazole to bobwhite quail and mallard duck submitted under current submissions (2002-3298/3299) were considered as supplemental to the previously submitted and reviewed reports. No NOEC could be determined from either of these studies.

Tebuconazole is categorized as practically non-toxic ($LD_{50} > 2000$ mg a.i./kg bw) to wild mammals on an acute oral basis in accordance with the USEPA descriptive categorization (1985c). Tebuconazole was of low acute dermal toxicity ($LD_{50} > 5000$ mg a.i./kg bw) and inhalation toxicity ($LC_{50} > 0.371$ and > 5.093 mg a.i./L for aerosol and dust, respectively) to rats as well as minimally irritating to rabbit eyes. It was not skin irritant or skin sensitizer.

The formulated end-use product, Folicur 432F Foliar Fungicide (40.6% technical), was of low acute oral (male $LD_{50} = 3776$ mg/kg bw, female $LD_{50} = 3710$ mg/kg bw, combined $LD_{50} = 3743$ mg/kg bw); dermal ($LD_{50} > 2011$ mg/kg bw); and inhalation toxicity ($LC_{50} > 2.51$ mg/L) to rats. Folicure 3.6 F was minimally irritating to rabbit eyes, slightly irritating to rabbit skin, and was not considered as a dermal sensitizer in guinea pigs.

Short-term oral studies (28-d and 90-d) on rats indicated that the liver and spleen were the organs mainly affected. The short-term dietary NOEL value for the 28 days toxicity study on rat was 30 mg a.i./kg bw/day (for both sexes), and the corresponding value for the 90-day toxicity study on rat was 100 ppm (7.5 mg a.i./kg bw/day in male and 9.4 mg a.i./kg bw/day in female).

In both the 90-day and 1-year dietary studies in dogs, tebuconazole had some effects on the lens of the eyes (cataracts and degeneration of the lens). The liver, spleen and adrenals were also affected. The NOELs were set at 200 ppm (7.2 mg a.i./kg bw/day for male and 7.7 mg a.i./kg bw/day for female) for the 90 days dietary dog study, and 100 ppm (2.96 mg a.i./kg bw/day, male/female) for the 1-year dietary dog study. In an another 1-year dog study, the NOEL was established at 200 ppm (6.4 mg a.i./kg bw/day, male/female).

In dermal studies, no systemic toxicity was noted in treated rabbits in a 3-week study. The NOEL was > 250 mg a.i./kg bw/day. In an another 3-week dermal toxicity study in rabbits, the NOEL was established at 1000 mg a.i./kg bw/day (the only dose tested) without any systemic toxicity.

In a 3-week inhalation study, a NOEL of 0.156 mg a.i./L/day (equivalent to 42.3 mg/kg bw/d) was established for rats based on clinical signs and increased liver enzymatic activities observed at the highest dose level (0.156 mg a.i./L).

The carcinogenic potential of tebuconazole was studied in rats and mice. In a chronic/ carcinogenicity study in rats (2-year dietary study), there was no evidence of carcinogenicity at dose levels up to and including 1000 ppm (male = 55 mg a.i./kg bw/day, and female = 86.3 mg a.i./kg bw/d). A NOEL for chronic toxicity was set at 100 ppm (male = 4.7 mg a.i./kg bw/day, and female = 6.5 mg a.i./kg bw/day) based on the treatment related effects on the spleen, liver, and adrenal glands. In chronic/carcinogenicity studies with mice, a NOEL of 60 ppm (18.2 and 26.1 mg a.i./kg bw/day for male and female, respectively) was set based on the treatment related effects on the liver. No increase in tumor incidences, however, was reported.

In a multigeneration reproductive study with the rat, the NOEL value was reported as 300 ppm (24.4 mg a.i./kg bw/day for male and 30.9 mg a.i./kg bw/day for female, respectively) for both parental and pup effects. In a developmental toxicity study on the mouse, the NOEL values were set at 10 and 3 mg a.i./kg bw/day, based on the maternal systemic effects (effects on liver enzyme and mild liver vacuolization) and developmental effects (incidences of sever external and visceral malformation), respectively. For rabbit, the corresponding values were 25.8 and 30 mg a.i./kg bw/day (maternal systemic effects), and 25.8 and 10 mg a.i./kg bw/day (developmental effects). The results of these developmental toxicity studies indicated that tebuconazole has a teratogenic potential and can increase fetal sensitivity in mice and rabbits.

In dermal studies on rat treated with technical tebuconazole at concentration up to 1000 mg a.i./kg bw/d, NOELs of 1000 mg a.i./kg bw/day for maternal systemic effects, < 1000 mg a.i./kg bw/day for maternal dermal effects, and 1000 mg a.i./kg bw/day for developmental effects were set. No signs of systemic toxicity and no developmental adverse effects were noted.

Genotoxicity/mutagenicity tests showed a negative response.

In an acute neurotoxicity study on rats, the signs of neurotoxicity (increased motor/locomotor activity) were noted on day zero (all rats recovered on day 7) of the treatment at 500 mg a.i./kg bw, and 6 out of 12 males died on day 1–2 of the 1000 mg/kg bw treatment. The NOEL was set at 100 mg/kg bw/day. In a subchronic neurotoxicity study on the rat, the NOELs of 400 ppm (male = 29.2 mg a.i./kg bw/day, and female = 34 mg a.i./kg bw/day) and 1600 ppm (male = 107 mg a.i./kg bw/day, female = 122 mg a.i./kg bw/day) were set for systemic toxicity and neurotoxicity, respectively. No treatment related neurotoxicity was observed in this study. In a developmental neurotoxicity study on the rat, NOEL of 300 ppm (22 mg a.i./kg bw/day) was set for both systemic and developmental toxicity. No treatment related neurotoxicity was observed at treatment levels up to 1000 ppm, the highest dose tested, and the NOEL was set at 1000 ppm (65 mg a.i./kg/day).

The effect of Folicur 432F Foliar Fungicide was assessed on seedling emergence and vegetative vigour of six dicot species and four monocot species (Tier 1). There were no adverse effects on the percentage of seedling emergence (number of seeds planted per replicate/number of plants emerged × 100) of any of the ten species tested. Soybean and tomato height as well as dry weight were inhibited as compared to the pooled controls (42% and 36% for soybean height and dry weight, respectively; and 34% and 50% for tomato height and dry weight, respectively). Phytotoxicity rating results for the seedling emergence test indicated significant phytotoxicity for soybean (50%), tomato (48%), and turnip (41%) (a significant phytotoxic effect was defined as greater than or equal to a 25% phytotoxicity rating). The most sensitive endpoints for soybean, tomato and turnip were phytotoxicity, weight and phytotoxicity, respectively. No adverse effects were observed in the vegetative vigour test for all crops tested.

The Tier 2 study was conducted on seedling emergence of soybean, tomato and turnip. There were no adverse effects on seedling emergence or percentage survival for these crops. The NOEC for these endpoints was considered as 453 g a.i./ha, with both an effect concentration 25% (EC_{25}) and 50% (EC_{50}) of > 453 g a.i./ha for all three crops.

For the effect of the compound on height, the NOEC of 227 g a.i./ha was set for soybean with the EC_{25} and EC_{50}, both at > 453 g a.i./ha. The NOEC of 57 g a.i./ha was set for both turnip and tomato. The turnip EC_{25} and EC_{50} were both > 453 g a.i./ha. The tomato was the most sensitive crop for this endpoint with an EC_{25} of 291 g a.i./ha and an EC_{50} of > 453 g a.i./ha.

There were no statistically significant differences in dry weight, as compared to the controls ($p > 0.05$), for soybean; therefore, the NOEC was considered as 453 g a.i./ha, with both an EC_{25} and EC_{50} of > 453 g a.i./ha. For turnip, the NOEC, EC_{25} and EC_{50} were determined to be 227, 416 and > 453 g a.i./ha, respectively. Tomato was the most sensitive crop of those tested. The NOEC, EC_{25} and EC_{50} were considered to be 57, 102 and 341 g a.i./ha, respectively.

The phytotoxicity NOEC for tomato, turnip and soybean was 113 g a.i./ha. The EC_{25} and EC_{50} for soybean and turnip were > 453 g a.i./ha. The tomato was the most sensitive crop tested, based on phytotoxicity, with an EC_{25} and EC_{50} of 398 and > 453 g a.i./ha, respectively.

These toxicity studies were classified as supplementary and they satisfy the guideline requirement for seedling emergence (Tier 1 and 2) toxicity study, pending submission of a new study incorporating the effects of the recommended non-ionic surfactants.

Data on the toxicity of tebuconazole to terrestrial organisms are summarized in Appendix IV, Table 11.

6.2 Effects on Aquatic Organisms

Acute Toxicity to Freshwater Organisms

In an acute toxicity study on *Daphnia magna*, the NOEC value of tebuconazole was considered to be 0.74 mg a.i./L based on mortality and other unspecified effects.

A 96-h LC_{50} of 4.4 mg a.i./L and 5.7 mg a.i./L were reported for rainbow trout and bluegill sunfish, respectively. The corresponding NOECs were reported as 1.5 mg a.i./L and < 1.4 mg a.i./L. Therefore, tebuconazole is categorized as moderately toxic ($1 < LC_{50} \leq 10$ mg/L) to freshwater fish in accordance with the USEPA's descriptive categorization (USEPA 1985d).

In a growth inhibition study with the green alga (*Scenedesmus subspicatus*), the following values were reported: a 96-h EC_{50} for biomass of 1.64 mg a.i./L; a 96-h EC_{50} for growth rate of 4.01 mg a.i./L; an NOEC for biomass of 0.32 mg a.i./L; an NOEC for growth rate of 1.0 mg a.i./L.

In a 4-day acute toxicity study with the green algae (*Selenastrum capricornutum*), the NOEC, EC_{25}, and EC_{50} values based on cell density were 2.46, 1.96, and 2.83 mg a.i./L, respectively.

In a 14-day acute toxicity study, the freshwater floating aquatic vascular plants, duckweed (*Lemna gibba* G3), were exposed to Folicur technical. The 14-day NOEC, EC_{25}, and EC_{50} values based on frond number were 62.3, 91.2 and 144.4 µg a.i./L, respectively. The 14-day NOEC, EC_{25} and EC_{50} values based on biomass (dry weights) were 62.3, 96.7 and 179.8 µg a.i./L, respectively.

Acute Toxicity to Estuarine/marine Organisms

Technical tebuconazole is categorized as highly toxic ($0.1 < LC_{50} \leq 1$ mg/L) to estuarine/marine crustaceans in accordance with the USEPA descriptive categorization (USEPA 1985e). The reported LC_{50} and NOEC values for mysid shrimp were 0.45 and < 0.30 mg a.i./L, respectively.

Based on the results of the Eastern oyster study, the LC_{50} and NOEC values for average shell growth were determined to be 3.0 and 1.7 mg a.i./L, respectively. Based on the results of this study, tebuconazole is categorized as moderately toxic ($1 < LC_{50} \leq 10$ mg/L) to estuarine/marine mollusks in accordance with the USEPA descriptive categorization (USEPA 1985f).

Chronic Toxicity to Freshwater Organisms

In a chronic effects study (21-day) of technical tebuconazole to daphnids, an EC_{50} and NOEC of 0.33 and 0.12 mg a.i./L were reported.

The reported NOEC in an early life stage toxicity study with rainbow trout (*Oncorhynchus mykiss*) was 12 µg a.i./L, based on the abnormal appearance and behaviour of the larvae (dark colouration and loss of equilibrium).

Chronic Toxicity to Estuarine/Marine Organisms

The 203-day (full life cycle) chronic toxicity of HWG 1608 to sheepshead minnow (*Cyprinodon variegatus*) was studied under flow-through conditions. The NOECs_{Fo} generation, based on adverse effects on length and reproduction, were considered to be 43.6 and 96.7µg a.i./L, respectively. The $LC_{50\ \text{Fl generation}}$ was > 97.8 µg a.i./L and the $\text{NOECs}_{\text{Fl generation}}$, based on mortality and adverse effects on hatching success were 97.8 and 97.8 µg a.i./L, respectively. Based on the results of this study, growth (length at day 33) of the F_0 generation was the most sensitive endpoint (NOEC = 43.6 µg a.i./L).

Data on the toxicity of tebuconazole to aquatic organisms are summarized in Appendix IV, Table 12. In the aquatic environment, tebuconazole readily partitions from water to sediments (up to 59% and 63% under aerobic and anaerobic conditions, respectively), where it persists (as described in Section 5.8). Therefore, a study of the toxicity of tebuconazole to a sediment dwelling aquatic organism is required.

6.3 Effects on Biological Methods of Sewage Treatment

Data are not required.

6.4 Risk Characterization

6.4.1 Environmental Behaviour

Abiotic transformation is not an important route of transformation of tebuconazole in the environment. Tebuconazole is stable to hydrolysis as well as photolysis on soil and in water. The photolytic DT_{50} of tebuconazole in soil and water were determined to be 191 and 590 days, respectively. The vapour pressure and Henry's law constant indicate that tebuconazole is non-volatile under field conditions.

Tebuconazole is classified as persistent in both the terrestrial and aquatic environment. The DT_{50} of this compound is calculated to be 770 days in aerobic soil. An acceptable anaerobic soil biotransformation study was not available, but the results of an unacceptable study and the aerobic soil, aerobic and anaerobic aquatic biotransformation studies indicated that tebuconazole will persist in anaerobic environment. The DT_{50} of tebuconazole in the aqueous systems (whole system) is 866 and 1386 days under anaerobic and aerobic conditions, respectively. In the aquatic environment, tebuconazole readily partitions from water to sediments (up to 59% and 63% under aerobic and anaerobic conditions, respectively), where it persists.

Tebuconazole shows low to moderate mobility in environmental compartments. The adsorption/desorption studies indicate that tebuconazole has low to moderate mobility ($K_{oc\text{-}ads} = 462–1251$) in soils according to the classification of McCall et al. (1981). Once adsorbed, the desorption process will be slower than the adsorption process as indicated by the larger K_{oc} values ($K_{oc\text{-}des} = 1237–2300$). There is a correlation between adsorption of tebuconazole and the soil content of clay because larger amounts of tebuconazole adsorbed to the soil having a higher content of clay.

The soil TLC (Rf values of 0.09–0.22) and aged soil column leaching studies indicated that tebuconazole has a low potential for mobility in soil. Less than 1% of the radioactivity leached through the column (44.5 cm in length), and most of the recovered radioactivity was identified as tebuconazole and found in the 0 to 24 cm segment. The vapour pressure and Henry's law constant indicate that tebuconazole is not likely to volatilize under field conditions.

Adsorption / desorption results for triazole, identified by the applicant as a transformation product, on a range of soils showed that tiazole has very high to high mobility in soil

(K_{oc-ads} = 21.1–126.7) according to the classification of McCall et al. (1981). Triazole, however, was not detected as major transformation product in any submitted abiotic and biotic laboratory studies.

An acceptable Canadian field dissipation study was not submitted at this time. Based on the weight of evidence from the unacceptable field dissipation studies (DT_{50}s = 205–912 days) that were submitted under submission numbers 1989-0604 and 1991-0524, the results from field studies that were conducted in the United States (DT_{50}s = 81–857 days) and the results from laboratory studies on biotransformation (DT_{50} = 770 days in soil), it is concluded that tebuconazole will be persistent and there is a potential for carryover to the subsequent growing season. Currently, the applicant is conducting a multiyear field study with anticipated completion in December 2004. A full assessment of the subject product will be conducted after the registrant submits this study.

Tebuconazole and its metabolites are not expected to bioaccumulate in terrestrial or aquatic organisms, based on lack of bioaccumulation as well as rapid depuration of tebuconazole in earthworm and bluegill sunfish. The BAFs for the earthworm as well as edible, viscera and whole fish were reported to be 1.35, 13, 150 and 78, respectively. The major metabolite identified in bluegill sunfish was a glucuronic acid conjugate of t-butyl hydroxy tebuconazole representing 63.1% and 58.6% on day 28 and day 35 in the viscera. The DT_{50} for depuration of the accumulated radiolabel in earthworm and bluegill sunfish were between one and three days. These studies indicate that tebuconazole is readily accumulated in earthworm and bluegill sunfish and is rapidly depurated; therefore, it is unlikely to bioaccumulate.

6.4.2 Terrestrial Organisms

Earthworms
Based on the comparison of the calculated EEC in soil (0.056 mg a.i./kg dry soil) and the LC_{50} and NOEC (1381 mg a.i./kg soil and 178 mg a.i./kg soil, respectively) the lethal and sublethal risk of tebuconazole to earthworm is negligible. The short-term risk quotient (RQ) values for earthworm mortality and sublethal effects are 0.0000406 (EEC/LC_{50}) and 0.000315 (EEC/NOEC), respectively.

Honeybees
Honeybees are important pollinators and they can be exposed to tebuconazole from direct application or contact with treated plant material. According to the classification by Atkins et al. (1981), tebuconazole is classified as relatively non-toxic to honeybees (contact LD_{50} > 10.99 µg a.i./bee). The contact LD_{50} was determined to be 176 µg a.i./bee. The contact toxicity RQ for bees is 0.000 63 (EEC/LD_{50}), where EEC is the proposed label rate of 0.126 kg/ha. LD_{50} of 176 µg a.i./bee was converted to kg/ha by multiplying µg a.i./bee by 1.12 (176 µg a.i./bee × 1.12 = 197.12 kg a.i./ha, EEC/LD_{50} = 0.126/197.12 = 0.00063). Therefore, the risk of tebuconazole to honeybees is negligible.

Birds
The possibility that birds will be exposed to tebuconazole (directly or indirectly) cannot be ruled out. Birds may be exposed to tebuconazole mainly by the consumption of contaminated feed. The risk assessment procedure is directed at risks to individuals as there are currently no commonly used criteria for judging the significance of effects for population level processes.

In the assessment of the acute oral risk to birds, the reviewer used the data for the female birds in the acute oral toxicity study. Based on the food consumption (FC) of 0.0152 kg dw/ind/d and body weight per individual (bw/ind) of 0.17 kg bw/ind, the daily intake (DI) was calculated as 0.34 mg a.i./ind/d. The LD_{50} and NOEC values were > 1200 and 432 mg a.i./kg bw. Based on the DI, the maximum number of days of intake of tebuconazole by a wild bird equivalent to a dose administered by a gavage that killed 50% of individuals in the laboratory population is equal to 608 days. The maximum number of days of intake of tebuconazole by a wild bird equivalent to the dose administered by gavage that had no NOEC on the laboratory population is 219 days. Therefore, the acute oral risk of tebuconazole to wild birds is expected to be negligible for the proposed use.

The dietary RQ values for bobwhite quail mortality and sublethal effects are 0.00441 (EEC/LC_{50}) and 0.0679 (EEC/NOEC), respectively. The corresponding RQ values for mallard duck are 0.000885 and 0.000885, respectively. Therefore, the risk of lethal and sublethal effects of tebuconazole to birds is negligible (RQ < 0.1) following dietary exposure.

The reproductive RQ value (EEC/NOEC) is 0.0562 for mallard duck, while the RQ for effects on bobwhite quail, based on neurological effects on parent birds, is 1.2. Therefore, the risk of reproductive effects of tebuconazole to mallard ducks is negligible, while the risk of adverse effects on bobwhite quail is moderate. Thus, the risk of adverse chronic effects to birds is moderate.

The initial risk assessment for avian effects was conducted using conservative exposure scenarios. Using these scenarios, it was determined that, the risk of acute effects of tebuconazole to birds is negligible, following oral and dietary exposure. The risk of adverse chronic effects to birds is moderate.

For chronic/reproductive effects on bobwhite quail, there is uncertainty regarding the endpoint used in the risk assessment. This uncertainty arises from the determination and interpretation of the NOEC of 18.4 mg/kg (based on neurological disorder) of an old study submitted earlier (Report No. 96776, 1988, EAD review, submission numbers 89-0604/0605). The incidences of nervous disorder, which were observed only in treatment groups (one bird in each treatment group was affected), may or may not have been related to tebuconazole exposure. The reviewer of the study assumed that neurological disorder was caused by tebuconazole exposure because it was only observed in the treatment groups and not in the control group. Such incidences were not reported in the mallard duck reproduction study or in the supplementary studies conducted on bobwhite quail and mallard duck at much higher concentrations (up to 290 mg a.i./kg). No NOEC, however, could be determined in the supplementary study on bobwhite quail because the adverse effects of tebuconazole on the reproductive parameters (reduced hatchling and 14-day survivor body weight) were reported at the lowest test concentration of 156 mg/kg diet. Neurological disorder was also reported in mammals (acute neurotoxicity study on rat).

Given these uncertainties around the effect endpoints, it is concluded that the risk of chronic/reproductive effects for the proposed use pattern can not be adequately characterized at this time.

Based on these considerations, a new study on chronic/reproductive effects of tebuconazole on bobwhite quail is required. The study should be conducted over a much wider range of concentrations, which is more realistic for the proposed use pattern.

Small Wild Mammals

Wild mammals could be exposed to residue of tebuconazole as a result of the consumption of sprayed vegetation and/or contaminated prey. As with birds, the risk assessment procedure is directed at risks to individuals. The EECs of tebuconazole in the diet of rat and mouse were 63.57 and 63.18 mg a.i./kg dry weight diet, respectively, based on the maximum application rate of 126 g a.i./ha.

In the assessment of the acute risk to rats, default values were used for FC (0.060 kg dw/ind/d) and body weight per individual (BWI) (0.35 kg bw/ind) (USEPA 1988). The DI was calculated as 3.81 mg a.i./ind/d. The LD_{50} was 2850 mg/kg bw for tebuconazole. As a NOEL was not available, one-tenth of the LD_{50} was used. Based on the DI, the maximum number of days of intake of tebuconazole by a rat equivalent to a dose administered by a gavage that killed 50% of individuals in the laboratory population is equal to 262 days. The maximum number of days of intake of tebuconazole by a rat to reach the NOEL is 26.2 days.

In the assessment of the acute risk to mice, default values were used for FC (0.0060 kg dw/ind/d) and BWI (0.033 kg bw/ind) (USEPA 1988). The DI was calculated as 0.38 mg a.i./ind/d. The LD_{50} was 4000 mg/kg bw for tebuconazole. As a NOEL was not available, one-tenth of the LD_{50} was used. Based on the DI, the maximum number of days of intake of tebuconazole by a mouse equivalent to a dose administered by a gavage that killed 50% of individuals in the laboratory population is equal to 348 days. The maximum number of days of intake of tebuconazole by a mouse to reach the NOEL is 35 days.

In the assessment of the acute neurotoxicity to rats, the maximum number of days of intake of tebuconazole by a rat to reach the NOEL for neurotoxicity was 9.2 days. This result was based on the default values for FC and BWI, as mentioned above, the calculated DI of 3.81 mg a.i./ind/d and the NOEL of 100 mg/kg bw. Therefore, the acute risk to small wild mammals is expected to be negligible for the proposed use.

Short-term dietary studies were conducted with tebuconazole on both rats and mice. The most sensitive and appropriate NOEL was 7.5 mg/kg bw/d, based on 90 days dietary study results. The RQ was calculated to be 8.5 for rat. This indicates a moderate risk for small wild mammals based on short-term dietary study.

In the assessment of the reproduction studies, the most sensitive and appropriate NOEL was 3 mg/kg bw/d, based on the teratogenic effects and increase fetal sensitivity in mouse. The RQ value was calculated to be 21.1. This indicates a high risk for small wild mammals based on teratogenic effects.

Terrestrial Plants

In the seedling emergence toxicity test (Tier 2) with terrestrial plants, the most sensitive endpoint was weight of tomato (NOEC 57 and EC_{25} 102 g a.i./ha). The EC_{25} 102 g a.i./ha was compared to the EEC resulting from one application of the Folicur 432F Foliar Fungicide (126 g a.i./ha) and the RQ (EEC/EC_{25}) value was calculated as 1.2, indicating a moderate risk to terrestrial plants. No vegetative vigour adverse effects were observed at the highest concentration tested (453 g a.i./ha).

The proposed end-use product, Folicur 432F Foliar Fungicide, is recommended to be used with a registered non-ionic surfactants, such as Agral 90 or AgSurf. These surfactants were not included in the subject studies. Addition of adjuvant/surfactant to the formulation or tank mix may enhance or modify the physical or chemical characteristics of a control product. Consequently, they alter the phytotoxicity effects of the pesticide. According to the USEPA's Ecological Effects Test Guidelines OPPTS 850.4000, *Background—Nontarget Plant Testing* (USEPA 1996a) and OPPTS 850.4225, *Seedling Emergence, Tier II* (USEPA 1996b), if an adjuvant is recommended on the product label, representative adjuvant must be included in the test at the recommended dosage. Trials that compare results from the use of the pesticide plus adjuvant or surfactant against results from the use of the pesticide alone, untreated control and/or a control with adjuvant/surfactant alone must be submitted.

An assessment of the environmental safety associated with the use of tebuconazole and its end-use product, Folicur 432F Foliar Fungicide, identified negligible risk to terrestrial invertebrates (earthworm and bees), as well as birds and small wild mammals on an acute basis. The risk to bobwhite quail was determined to be moderate on a reproductive basis. The risk to small mammals was determined moderate to high on a short-term dietary and chronic/reproductive basis. The risk to vascular plants was moderate. The risk of tebuconazole to terrestrial organisms is summarized in Appendix IV, Table 14.

6.4.3 Aquatic Organisms

Although the proposed use does not include direct application to water, the possibility that aquatic organisms will be exposed to tebuconazole, directly or indirectly, cannot be ruled out. The aquatic EEC value for tebuconazole was 0.042 mg a.i./L.

Acute toxicity to Freshwater Organisms

Based on the comparison of the calculated EEC in water (0.042 mg a.i./L) and the LC_{50}/EC_{50} as well as the NOEC of the acute toxicity studies to freshwater organisms, corresponding RQ values were calculated to be < 0.1. These values indicate that the acute lethal and sublethal risk of tebuconazole to freshwater organisms is negligible.

Acute Toxicity to Estuarine/Marine Organisms

The RQ values for mysid shrimp and Eastern oyster are in the range of < 0.1 and ≥ 0.1–1, indicating a negligible to low risk to estuarine/marine invertebrates on an acute basis.

Chronic Toxicity

The RQ values for long-term exposure indicate that low risk to invertebrates and moderate risk to early life cycle of freshwater fish (RQs 0.35 and 3.5 for daphnid and early life cycle of rainbow trout, respectively) is expected. Risk of chronic effects on marine fish is low (RQ 0.963 for chronic study on sheepshead minnow).

An assessment of the environmental safety associated with the use of tebuconazole and its end-use product, Folicur 432F Foliar Fungicide, identified negligible risk to freshwater organisms on an acute basis. The risk was determined to be low to moderate to freshwater invertebrates and fish, respectively, on a chronic basis. A negligible to low risk to estuarine /marine organisms was determined on an acute and chronic basis. The risk of tebuconazole to aquatic organisms are summarized in Table 15 of Appendix IV.

6.5 Outstanding Data Requirements

DACO 8.3.2.1	Canadian field dissipation study. The applicant is conducting a multiyear field study with anticipated completion in December 2004.
DACO 9.3.4	Chronic toxicity study of tebuconazole to a sediment dwelling aquatic organisms. In aquatic environment, tebuconazole readily partitions from water to sediments, where it persists.
DACO 9.5.2.4	Acute study on marine/estuarine fish.
DACO 9.6.3.1	Study on chronic/reproductive effects in bobwhite quail. This study **must** cover the systemic toxicity, neurotoxicity and developmental/reproduction toxicity on the birds. The study should be conducted over a much wider range of concentrations, which is more realistic for the proposed use pattern. The registrant should submit a draft protocol of the study for comments by the PMRA prior to initiation of the study.
DACO 9.8.4	Seedling emergence toxicity study on vascular plant (Tier 2). The proposed end-use product, Folicur 432F Foliar Fungicide, is recommended to be used with a registered non-ionic surfactants, such as Agral 90 or AgSurf. These adjuvant **must** be included in the test at the recommended dosage. Trials must compare results from the use of the pesticide plus adjuvant or surfactant against results from the use of the pesticide alone, untreated control and/or a control with adjuvant/surfactant alone.

6.6 Risk Mitigation

Based on the data submitted and using a scenario of the maximum application rate of 126 g a.i./ha, an assessment of the environmental safety associated with the use of the technical grade active ingredient tebuconazole and the formulated EP Folicur 432F Foliar Fungicide has identified the following risks:

- high risk of chronic/teratogenic and moderate risk of short-term dietary toxic effects on small wild mammals;
- moderate risk of chronic toxic effects on birds (bobwhite quail);
- moderate risk of chronic toxic effects on freshwater fish; and
- moderate risk on terrestrial vascular plants.

The proposed technical and formulated labels provided the precautionary language regarding the safe procedure for use, storage and disposal, or spill of the products. Also, the proposed label of the formulated product, Folicur 432F Foliar Fungicide, recommends applying the product only in alternate years in fields adjacent to aquatic areas and not cultivating within 3 metres of an aquatic area to allow growth of a vegetative filter strip as well as a 30-metre buffer zone for aquatic areas.

Based on the adverse effects predicted for the product (persistence and carryover, adverse chronic effects on bird, small wild mammals as well as aquatic organisms), environmental hazard statements and some restrictions are required on the label for the protection of non-target terrestrial and aquatic habitats. However, no buffer zones are required. It is recommended that Folicur 432 F Foliar Fungicide be applied in alternate years at all locations it is used, not only in fields adjacent to aquatic areas.

a) Tebuconazole Technical Label

The precautionary labelling under **ENVIRONMENTAL HAZARDS** should be replaced with the following:

> **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

b) Folicur 432F Foliar Fungicide Label

Under **DIRECTION FOR USE**, field sprayer application:

> **DO NOT** apply during periods of dead calm or when winds are gusty. **DO NOT** apply with spray droplets smaller than the ASAE medium classification.

Under **DIRECTION FOR USE**, aerial application:

> **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the ASAE medium classification.
>
> When a tank mixture is used, consult the labels of the tank mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

The general instructions for aerial application as per DIR96-04 should be added to the label.

Under **ENVIRONMENTAL HAZARD** replace the existing statements with the following:

> Tebuconazole is persistent and will carryover. It is recommended that any products containing tebuconazole not be used in areas treated with this product during the previous season, i.e., this product should be used only in alternate years.
>
> Toxic to birds, small wild mammals, aquatic organisms and non-target plants. **DO NOT** apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Runoff is hazardous to aquatic organisms in neighbouring areas. **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes. To reduce the run off, refer to the recommendation under **APPLICATION IN FIELDS ADJACENT TO AQUATIC AREAS**.

Under **APPLICATION IN FIELDS ADJACENT TO AQUATIC AREAS** add the following:

> **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.
>
> To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to heavy rainfall, moderate to steep slope, bare soil, poorly drained soil (e.g., soils that are compacted or fine textured). Avoid application of this product when heavy rain is forecast.

Under title "WIND" change the wind speed to "greater than 16 km/h".

Buffer Zones

The buffer zones for aquatic environments (freshwater and marine/estuarine) were calculated using NOEC for the most sensitive non-target aquatic organisms (NOEC 0.012 mg a.i./L for rainbow trout and NOEC 0.044 mg a.i./L for sheepshead minnow), and EECs were calculated using the standard PMRA overspray scenario. Buffer zones for the terrestrial environment were calculated using the EC_{25} for the most sensitive terrestrial organisms. Spray drift information from Wolf and Caldwell (2001) was used to calculate the buffer zones for ground applications on field crops. The AGDISP model version 8.08 was used to calculate the buffer zones for aerial application. Based on the results of these calculation no buffer zones are required for Folicur 432 F Foliar Fungicide. The current draft label for the Folicur 432F Foliar Fungicide has recommended a 30-metre buffer zone adjacent to aquatic areas. This statement is not required but is acceptable (Science Review Committee recommendation).

7.0 Efficacy

7.1 Effectiveness Against Target Organisms or with Respect to the Effect Achieved

7.1.1 Intended Use

Table 7.1.1 Folicur 432F Foliar Fungicide for Suppression of Fusarium Head Blight and Control of Foliar Diseases in Wheat (spring wheat, winter wheat and durum wheat)

Product Name	Application Rate per Hectare		Application Timing
	Product (mL/ha)	Active ingredient (g a.i./ha)	
Folicur 432F Foliar Fungicide	292	126	Late vegetative stage to 50% flowering

Table 7.1.2 Folicur 432F Foliar Fungicide plus Non-ionic Surfactant Agral or Agsurf

Product Name	Pest Control Product Registration No.	Recommended Application Rate (vol/vol)
Agral 90	11809, 24725	0.125
AgSurf	15881	0.125

7.1.2 Mode of Action

Tebuconazole, the active ingredient of Folicur 432F Foliar Fungicide, is a systemic fungicide with protectant, curative and eradicant action. It is a sterol biosynthesis inhibitor. It acts against target fungi by inhibiting the enzyme C_{14}-demethylase in the sterol-biosynthesis pathway (i.e., by inhibiting the C_{14} demethylation step). Tebuconazole is classified as a Group 3 Fungicide.

7.1.3 Description of Pest Problem

Fusarium Head Blight

Fusarium head blight (FHB, *Fusarium* spp.), also referred as scab, is a fungal disease of small-grain cereals and corn. Epidemics typically reduce yields. In very susceptible cultivars, 50–80% of developing spikelets can be damaged or killed before grain filling. *Fusarium* spp. also produce deoxynivalenol (DON, vomitoxin), a toxin that renders the grain unfit for human or animal feed. The acceptable DON level varies depending on the type of wheat. In general, when DON is greater than 1.0 ppm, it is unsuitable for human consumption. Mycotoxin contamination reduces grain marketability and often has a greater economic impact than loses in yield. Agriculture and Agri-Food Canada recommends no more than 5 ppm DON in rations for cattle and poultry. Swine are particularly sensitive to DON and the recommended level in hog rations is not to exceed 1 ppm. The severity of FHB infection varies greatly from year to year as weather plays a crucial role on the infection process. Wet weather during flowering is generally enough to initiate epidemics. If the weather is dry during this period, the crop will remain essentially free of *Fusarium* damage.

Fusarium head blight is found on a wide range of hosts, including wheat, barley, oat, corn, rye and wild grass species. The species involved in FHB are capable of infecting all plant parts. Infection of the crown and root tissues may coincide with head blight. In North America, the predominant and most aggressive species causing FHB is *Fusarium graminearum* and increasingly becoming a problem in Canada. Before 1993, frequent outbreaks were reported from Ontario, Quebec and the Maritimes. The disease has since become a problem in Manitoba, where annual losses of $50 million have been reported.

It has occurred at low to moderate levels in southeastern Saskatchewan since 1998. *Fusarium* spp. overwinter on seeds and crop residues. Infected host residues, especially those of corn and small grain cereals, serve as the source of inoculum, especially later in the season. Young cereal seedlings are often infected at the time of emergence. Ascospores produced on the residues at or close to the soil surface are believed to be the main source of inoculum. The incidence and severity of FHB thus appears related to the amount of primary inoculum available around the time of anthesis when infections are most frequent and severe. Infection is favoured by a combination of persistent wetness and moderately warm weather. Rain is required several days prior to heading to initiate spore release from the infected stubble. Perithecia absorb the moisture and burst, shooting out spores. As warm, moist weather develops, the spores are disseminated by wind and rain splashing and come into contact with the above-ground parts of the crop including the glumes, florets as well as other parts of the spike. Anthers seem to offer the initial point of infection by the attacking fungus. Symptoms of FHB appears after flowering, typically within three days, usually after a period of warm wet weather. The longer the period of wetness between anthesis and the soft dough stage, the greater the chance of infection and increased severity. The earlier a kennel becomes infected in its life cycle with FHB, the greater the effect will be. Infected wheat grain is typically small and shrunken as well as chalky-white to pink in colour.

Septoria Diseases—Leaf Blotch and Glume Blotch

Septoria diseases (*Septoria tritici*, *Stagonospora nodorum* or *Septoria nodorum*, *Stagonospora avenae*) occur on wheat and other small grains throughout Canada. The blotches on leaves may be similar to those caused by tan spot. Severity of diseases increases during wet growing seasons, results in shrivelled grain and depressed yield. Symptoms caused by *S. tritici* are yellow flecks first appearing on the lower leaves, especially those touching the soil. These develop into yellow, greyish white, or brown blotches on all above-ground plant parts. On leaves, yellow-bordered lesions are restricted by the veins and develop longitudinally with parallel sides and blunt ends. These elongated blotches eventually coalesce. Leaves infected at the base may be killed. Leaf lesions caused by *S. nodorum* are light with a dark margin. *S. nodorum* may also cause blotches on the glumes and nodes as plants mature. Glume infections often begin at the tips and spread downward as purplish brown to grey lesions with dark pycnidia. Kernels may be severely shrivelled, resulting in yield reductions that can be as high as 50%. The shrivelled grain is often associated with a lowered germination rate. Symptoms of *S. avenae* generally appear late in the season when plants are ripening. Premature leaf senescence is the typical result, but this does not cause significant yield losses. Initially, symptoms appear as small yellow flecks, which enlarge to become light brown oval or lens-shaped blotches about 5 mm in length often with a grayish-brown centre. A yellow margin often surrounds the margins.

The fungi are seedborne and overwinter on crop residue and winter wheat plants. Asexual spores initiate the disease in the fall (winter wheat) or spring. Abundant pycnidia are produced on necrotic leaves and glumes in wet weather. Conidia are dispersed in the crop by rain splash.

Tan Spot

Tan spot (*Pyrenophora tritici-repentis*) affects wheat worldwide. It is widespread on spring and winter wheat in Ontario and the Prairies. On susceptible wheat leaves, tan spot symptoms appears as oval to diamond-shaped lesions. Tan or brown flecks first appear on leaves. These flecks become lens-shaped, expand and coalesce. The centre of these larger spots becomes dark brown. A chlorotic halo usually surrounds the dark brown centres. Leaves that are severely infected may senescence prematurely and fall off. Wheat can be affected during grain filling. Infected seed is small and shrivelled, and may have pinkish colouration called red smudge. Infected seed is downgraded as the dark specks produced in the semolina cause an aesthetic defect in the pasta. Infected seed is also associated with reduced germination, reduced seedling emergence as well as seedling vigour and uneven crop stand. Tan spot affects grain yields by limiting tillering, leaf area index, dry matter accumulation and grain size. Yield reductions vary according to the timing and intensity of the disease as well as the susceptibility of cultivars. A reduction of 48% with tan spot has been reported.

Pyrenophora tritici-repentis overwinters on crop residues. During the growing season, conidia are produced in old lesions on wet leaves and become airborne as the leaves dry. Several cycles of conidial production may occur in a single growing season.

Leaf Rust

Leaf rust (*Puccinia recondita* f. sp. *tritici*) is the most common disease of wheat in the world and occurs annually across the wheat-growing regions of Canada. Leaf rust lesions are almost round, the size of pin head and confined mostly to the upper surfaces of leaves. They may also occur on the stem and leaf sheath, but do not penetrate the tissue there. They are yellowish-red, but darken and turn black as the plant mature. Heavily infected leaves may take on an orange-red appearance and die prematurely.

In North America, the persistence of leaf rust from year to year is due to overwintering of the uredinial stage on wheat in the southern United States and Mexico. The disease progresses northward each spring, producing cycles of urediniospores on sequentially maturing wheat crops. Disease development is favoured by heavy rains or by heavy dews produced by cool nights and warm days. Heavy rust infections, especially when they occur early, will result in premature leaf senescence and ultimately lower yields because of impaired grain filling and reduced kernel size. Yield losses can vary from 5% to 15%.

Stripe Rust

Stripe rust (*Puccinia striiformis*) has been known to cause serious yield losses in spring and winter wheat. The disease can cause yield losses of 75% in soft white spring wheat. The symptoms of stripe rust are elongate yellow pustules on leaves and heads. Pustules on leaves often extend the entire length of the leaf blade. Late in the season, the yellow urediniospores in the pustules are replaced by dark brown teliospores. Heavy infection results in defoliation and shrivelling of the seed. Stripe rust has no alternative host.

Puccinia striiformis overwinters as urediniospores or as dormant mycelium in leaves of native grasses and winter wheat in the United States. During mild winters, the fungus can survive on winter wheat in parts of Canada. In most summers, urediniospores are carried by air currents into the northern United States and Canada.

Stem Rust

Stem rust (*Puccinia graminis*) once was the most destructive disease of wheat in North America. The disease has been managed successfully through wheat breeding programs. Genes for resistance have been identified and incorporated into varieties to provide resistance against specialized, virulent races of stem rust.

Stem rust produces reddish-brown pustules on the leaves and especially the stems of susceptible wheat plants. As the plants mature, the pustules darken to become black. The disease begins in the spring in the southern United States and northern Mexico, where urediniospores and infective mycelium overwinter on winter cereals and wild grasses. Fresh spores are produced and carried northward by winds. As the pathogen moves north, it repeatedly infects susceptible winter and spring cereal crops. The severity of the disease depends on the amount, time of arrival and virulence phenotypes of inoculum from the United States, the susceptibility and growth stage of the crops, and weather conditions. Stem rust does not appear to overwinter much in Canada.

Powdery Mildew

Powdery mildew (*Erysiphe graminis* f. sp. *tritici*) affects wheat, barley as well as a number of grasses, mainly during dry cool seasons, and can cause considerable damage. The fungus is able to infect wheat at all growth stages between seedling emergence and maturity. Powdery mildew infections are initiated by wind-blown spores that land on susceptible plant tissues. The spores germinate and produce superficial patches of grayish-white, cottony mycelium and spores on the upper surfaces of leaves. The generation time of powdery mildew can be as short as 7–10 days, which can quickly lead to epidemics under optimum conditions. Because powdery mildew reduces the phytosynthetic area of the leaves, cereals infection with it may tiller less as well as fewer and smaller grains. Yield can be seriously affected if the flag and penultimate leaves are heavily infected. Severe, early infection can stunt wheat plants and even lead to the failure of plants to produce spikes.

7.1.4 Effectiveness Against Pests

Results were submitted from 89 field studies conducted in Canada and in the United States between 1996 and 2002 which assessed the performance of Folicur 432F Foliar Fungicide. The performance for suppression of Fusarium head blight was evaluated by disease incidence, disease severity (DS), FHB Index, percentage of *Fusarium* Damaged Kernels (FDKs), grain DON levels, and yield. Leaf damage caused by foliar diseases was evaluated by visually estimating the percentage incidence and the percentage of severity with typical symptoms for the target disease and yield.

7.1.4.1 Suppression of Fusarium Head Blight (*Fusarium* spp.)

A total of 35 efficacy studies were submitted to support the claim.

Disease Severity Reduction
Fusarium severity was recorded in 14 studies. The data showed a significant Fusarium severity reduction in eight studies, and a numerical reduction in the remaining six studies.

Twelve studies included a 1.5× rate (187 g a.i./ha) and 5 studies included a 0.5× rate (62.5 g a.i./ha). The data showed no significant differences among the three rates. However, the data did show a positive rate response to increased rate of tebuconazole, i.e., 64.0%, 72.4% and 83.2% disease reduction for the 0.5×, 1× and 1.5× rates, respectively.

Disease Incidence Reduction
Fusarium incidence was recorded in 13 studies. The data showed a significant incidence reduction in five studies and a numerical reduction in the remaining eight studies.

Eleven studies included a 1.5× rate (187 g a.i./ha) and five studies included a 0.5× rate (62.5 g a.i./ha). The data showed no significant differences among the three rates. However, the data did show a positive response to increased rate of tebuconazole, i.e., 61.3%, 64.5% and 70.8% reduction for the 0.5×, 1× and 1.5× rates, respectively.

FHB Index
FHB Index was recorded in 13 studies. The data showed a significant FHB Index reduction in five studies and a numerical reduction in the remaining eight studies.

Six studies included a 1.5× rate (187 g a.i./ha) and 5 studies included a 0.5× rate (62.5 g a.i./ha). The data showed no significant differences among the three rates. However, the data did show a positive rate response to increased rate of tebuconazole, i.e., 77.3%, 82.2% and 90.0% reduction for the 0.5×, 1× and 1.5× rates, respectively.

***Fusarium* Damaged Kernel**

The percentage of FDK were recorded in 14 studies. The data showed a significant FDK reduction in two studies and a numerical reduction in the remaining 12 studies.

Nine studies included a 1.5× rate (187 g a.i./ha) and 2 studies included a 0.5× rate (62.5 g a.i./ha). The data showed no significant differences among the 3 rates, i.e., 21.5%, 49.0%, 49.0% FDK reduction for the 0.5×, 1× and 1.5× rates, respectively.

Grain Mycotoxin Deoxynivalenol (DON) Reduction

In 21 studies, DON was recorded for 211 varieties. The data showed that DON level was reduced by 0–78%, with an average of 32.4% at the proposed rate of 126 g a.i./ha.

Thirteen varieties included a 1.5× rate (187 g a.i./ha) and one study included a 0.5× rate (62.5 g a.i./ha). The data showed that the proposed rate (1×) provided the highest DON reduction.

Sixty-four varieties had DON levels of 5.0–7.0 ppm in the untreated check. The data showed an average reduction of 29% with the application of Folicur at the proposed rate of 126 g a.i./ha. However, DON levels were not reduced below 1.0 ppm in any of these studies.

Thirty-seven varieties had DON levels at 2.0–5.0 ppm in the untreated check. The data showed an average reduction of 27% with the application of Folicur at 126 g a.i./ha. However, only 5 out of 37 varieties (14%) were reduced below 1.0 ppm.

Twenty-nine varieties had DON levels of 1.0–2.0 ppm in the untreated check. The data showed an average of 49% DON reduction with the application of Folicur at 126 g a.i./ha. Of these, 22 varieties (76%) were reduced below 1.0 ppm.

Sixty-eight varieties had DON levels between 0 and 1.0 ppm in the check. Of those, 2 varieties showed an increase in DON levels higher than 1.0 ppm.

Yield

Yield was recorded in all studies. The data showed a significant or numerical increase in yield after the application of Folicur. However, several other diseases were present, and the increase in yields may not necessarily be attributed solely to the control of FHB.

Timing of Application

The proposed application timing is from when at least 75% of the wheat heads on the main stem are fully emerged to when 50% of the heads on the main stem are flowering, or growth stage BBCH 61–65. Nine studies compared the proposed timing with an earlier application at BBCH

36–45. The data showed that the proposed timing consistently provided higher disease control than an early application.

The data support the proposed claim for suppression FHB on wheat, apply Folicur 432F Foliar Fungicide at 126 g a.i./ha (292 mL/ha) when at least 75% of the wheat heads on the main stem are fully emerged to when 50% of the heads on the main stem are flowering.

7.1.4.2 Control of Leaf Rust (*Puccinia recondita*)

Twelve studies were submitted to support this claim. Five studies were not reviewed because they were conducted under low disease pressure.

The remaining seven studies were conducted under adequate disease pressure. The surfactant AgSurf was added to the Folicur treatment. Disease severity and incidence on the flag and penultimate leaves, and yield were assessed. The data showed significant differences in disease severity and incidence between the treatments and the untreated check. The data also showed that Folicur at the proposed rate provided numerically higher rust control than the commercial standard, Tilt.

One study included a 1.5× the proposed rate (187 g a.i./ha). The data showed that the higher rate provided the same disease control level as the proposed rate (126 g a.i./ha). Two studies included a treatment of 0.5× rate (62.5 g a.i./ha), the data showed no significant difference between the proposed rate and the 0.5× rate. The lowest effective rate could not be established based on the available data.

The data support the proposed claim for control of leaf rust, apply Folicur + AgSurf at 126 g a.i. + 0.125% vol/vol per hectare.

7.1.4.3 Control of Stem Rust (*Puccinia graminis*)

Three studies were submitted to support the claim. A surfactant, either Induce or Tactice, was added to the Folicur treatment. Disease severity and incidence on flag and penultimate leaves, and yield were assessed. One study was not reviewed because it was conducted under low disease pressure and disease rating was not recorded.

Symptoms of stem rust are black red pustules forming on stems and, to a lesser extent, on leaves of susceptible plants (Bailey et al. 2003). The available studies assessed stem rust severity or incidence on the flag and penultimate leaves. They are considered appropriate because it is also accepted by other regulatory organizations. For example, the European and Mediterranean Plant Protection Organization Standard PP1 Vol. 2 on Efficacy Evaluation of Fungicides and Bactericides (EPPO 1997).

The data showed that Folicur significantly reduced rust incidence/severity and provided significantly better rust control than the commercial standard, Tilt.

The data support the proposed claim for control of stem rust, apply Folicur + Induce or Tactice at 126 g a.i. + 0.125% vol/vol per hectare.

7.1.4.4 Control of Stripe Rust (*Puccinia striiformis*)

Four studies were submitted to support the claim. AgSurf was added to Folicur treatment. Disease severity and incidence on the flag and penultimate leaves, and yield were assessed. The data showed that Folicur significantly reduced rust incidence/severity in three studies. In one study, Folicur did not provide adequate stripe rust control at the second rating. This is probably because the stripe rust appeared late in the growing season. The early application no longer provided control, and the late application was too late to provide any meaningful control.

The data support the proposed claim for control of stripe rust, apply Folicur + AgSurf at 126 g a.i. + 0.125% vol/vol per hectare.

7.1.4.5 Control of Septoria Leaf Blotch (*Mychsphaerella graminicola*, asexual state *Septoria tritici*)

Thirty-one studies were submitted to support the claim. A surfactant, AgSurf or Induce, was added to Folicur treatments in most studies. Disease severity and incidence on the flag and penultimate leaves, and yield were assessed. Twenty-one studies were not reviewed because they were conducted under very low disease pressure. The remaining ten studies were conducted under low to high disease pressure.

The data showed significant differences between the treatments and the untreated check in disease severity and incidence. Five studies included a commercial standard, Tilt. The data showed that Folicur provided numerically higher disease control in four studies.

Five studies included a treatment at 1.5× rate (187 g a.i./ha). The data showed no significant differences between the 1× and 1.5× rates. One study, conducted under low disease pressure, included a 0.5× rate. The data showed no difference between the proposed rate (126 g a.i./ha) and the 0.5× rate (62.5 g a.i./ha). The lowest effective rate could not be established based on the limited data.

The data support the proposed claim for control of Septoria leaf blotch, apply Folicur + AgSurf or Induce at 126 g a.i. + 0.125% vol/vol per hectare.

7.1.4.6 Control of Tan Spot (*Pyrenophora tritici-repentis*)

Five studies were submitted to support this claim. A surfactant, AgSurf or Merge, was added to the Folicur treatments in all studies. Disease severity and yield were assessed. The data showed a significant difference between the treatments and the untreated check. Three studies included a commercial standard, Tilt. The data showed that Folicur and Tilt provided the same level of disease control.

Two studies included a treatment at 1.5× rate (187 g a.i./ha). The data showed that the proposed rate and 1.5× rate provided the same level of disease control.

Two studies included a treatment at 0.5× rate (62.5 g a.i./ha). The data showed that the 0.5× rate did not provide adequate disease control in one study, and there was no difference in disease control in the other one while the proposed rate (126 g a.i./ha) provided effective control.

The data support the proposed claim for control of tan spot, apply Folicur + AgSurf or Merge at 126 g a.i. + 0.125% vol/vol per hectare.

7.1.4.7 Control of Powdery Mildew (*Erysiphe graminis* f. sp. *tritici*)

Nine studies were submitted to support the claim. Six studies were not reviewed because they were conducted under very low disease pressure.

The remaining three studies showed significant differences between the treatment and the untreated check. A commercial standard, Tilt, was included in all studies. The data showed that Folicur and Tilt provided the same level of disease severity/incidence control.

The data support the proposed claim for control of powdery mildew, apply Folicur alone or Folicur + AgSurf at 126 g a.i. + 0.125% vol/vol per hectare.

7.1.4.8 Comparison of Folicur Alone with Folicur plus Surfactant

Eleven studies were submitted to support the claim that the addition of surfactant to Folicur improves efficacy.

Two studies compared Folicur alone with Folicur + surfactant (AgSurf) for control of tan spot. The data showed no significant difference between the treatments, although the addition of AgSurf at 0.125% vol/vol numerically increased disease control in one study. These two studies also compared two surfactants at different rates. The data showed that the addition of AgSurf at 0.125% vol/vol provided the best disease control.

The remaining nine studies did not record disease incidence/severity, or yield. The percentage of disease reduction or percentage of yield increase was recorded. The data showed that the addition of surfactant consistently provided higher disease control and higher yield, indicating that the addition of a surfactant has value.

Among the non-ionic surfactants tested, only AgSurf is registered in Canada. Therefore, the claim for adding AgSurf is accepted. Agral 90, a non-ionic surfactant, is also registered in Canada, but was not tested in the studies. However, since the data demonstrated that the addition of AgSurf or other surfactants consistently provided higher disease control and higher yield, and that no adverse effects were observed, the claim for adding Agral 90 is also accepted.

7.1.4.9 Aerial Applications

Two studies were submitted to support the claim. One study recorded the percentage of FHB. The data showed that there is no difference in FHB reduction between ground and aerial application. All studies recorded yield. The data showed that the yield was consistently increased by Folicur application. However, all studies were conducted under low disease pressure. Confirmatory aerial studies, conducted under adequate disease pressure, are required.

Aerial application is conditionally accepted. Additional confirmatory aerial studies are required before this application method can be fully supported.

7.1.5 Total Spray Volume

Folicur 432F Foliar Fungicide should be applied in a minimum of 100 L of water per hectare by ground application or 47 L of water per hectare by aircraft application. Avoid excessive water volume (maximum 200 L) at flowering because this can increase the risk of infection.

7.2 Phytotoxicity to Target Plants or to Target Plant Products

In efficacy studies, Folicur applied at 1× or 1.5× rate (126 or 187 g a.i./ha) with or without a surfactant, at the proposed timing, resulted in yield increase in the majority of the studies. No phytotoxicity was noted for all the rates tested, indicating that Folicur has no adverse effects on wheat.

7.3 Impact on Succeeding Crops, Adjacent Crops and on Treated Plants or Plant Products Used for Propagation

7.3.1 Impact on Succeeding Crops

N/A

7.3.2 Impact on Adjacent Crops

N/A

7.3.3 Impact on Seed Viability

N/A

7.4 Economics

Not assessed.

7.5 Sustainability

7.5.1 Survey of Alternatives

There are a number of methods available to aid in controlling the establishment and spread of FHB (variety selection, crop rotation, residue management and clean seed) but once FHB has established itself in the wheat crop they will not help to control it's spread if the environmental conditions are favourable (Tenuta 2003; Manitoba Agriculture, Food and Rural Initiatives 2001). Therefore, FHB is particularly dependent on an integrated pest management (IPM) program.

The two most promising areas of alternative research are biological pesticides and resistant wheat varieties. None of these products are currently on the market.

The development of biological pesticides has focussed on the use of antagonists. There are two biological pesticides in the American pipeline, *Bacillus subtilis* GB03 (Kodiak) (USEPA 1999a), and *Bacillus subtilis* MBI 600 (Subtilex) (USEPA 1999b). These products are spore forming bacterium that compete with *Fusarium* and can be applied as a seed treatment as they will stay alive and grow after the seeds are planted. Some studies have shown up to a 96% reduction of disease severity and a 78% reduction in disease incidence using *Bacillus subtilis* (Schisler 2003).

There has also been research on biological control using *Trichoderma* sp., *Pseudomonas* sp., *Cyrptococcus* sp., *Stenotrophomonas* sp. and *Lyobacter* sp. or their biological active products that has shown to significantly reduce FHB disease and mycotoxin levels in both greenhouse and field trials (Dilantha Fernando 2003). *Pseudomonas chloroaphis* (PA-23) in particular has shown great promise (Dilantha Fernando 2001), showing consistent reduction of mycelial growth in lab studies and 23% less infected heads in greenhouse trials.

In Canada, the only alternatives available are IPM practices. When FHB is prevalent in an area, a partially resistant variety of wheat should be considered the following year. There are no totally resistant varieties available at this time. Crop rotation and residue management are the recommended tools. A non-host crop will reduce the level of inoculum in the field, infested cereal and corn residues are the primary source of inoculum and consecutive small cereal crops or corn should be avoided. Two years between these crops will allow for residue decomposition and reduce the inoculum in the field. Forecasting should be used in the control of FHB as the main precursor to FHB is prolonged wet and warm periods of weather. Many provinces have FHB forecasting. Fusarium free seed will also help reduce the occurrence of infection.

7.5.1.2 Chemical Control Practices

For the pest of greatest concern, FHB, one product is registered in Canada for its suppression. Bravo 500 (PCP 15723, chlorothalonil) has temporary registration until 31 December 2004. However, the performance of Bravo 500 is not consistent. Therefore, it has not been widely used. Folicur 432F Foliar Fungicide had emergency registration in certain areas of Canada in 2004. Another product, Proline (active ingredient prothioconazole), is currently under review. Other traditional pesticides are available in the United States or pending registration in Canada, such as prochloraz and prothioconazole JAU 6476.

For all other pests, there are alternatives, such as:

- Headline, (PCP 27322, pyraclostrobin);
- Flint (PCP 27529, trifloxytrobin);
- Stratego (PCP 27528, trifloxytrobin and propiconazole);
- Tilt (PCP 19346, propiconazole);
- Bravo 500 (PCP 15723 chlorothalonil); and
- Dithane (PCP 20553, mancozeb).

7.5.2 Compatibility With Current Management Practices Including Integrated Pest Management

Tebuconazole is compatible with current IPM practices for controlling FHB and the foliar diseases. Currently, partially resistant variety selection, crop rotation, residue management, clean seed (free of FHB) and forecasting can be used to control the establishment of FHB. However, this does not guarantee the crop will not become infected. If forecasting indicates the establishment of FHB is favourable, the use of a fungicide may help control the spread or severity of the infection.

7.5.3 Contribution to Risk Reduction

Tebuconazole is not a reduced-risk chemical. It can contribute to an IPM program as a complement to crop and residue management. Tebuconazole offers suppression of FHB, not control.

7.5.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

There are no reports of resistance to tebuconazole. Tebuconazole is a Group 3 fungicide. It has medium resistance risk of developing resistance.

Resistance Management Recommendations
For resistance management, please note that Folicur 432F Foliar Fungicide contains a Group 3 fungicide. Any fungal population may contain individuals naturally resistant to Folicur 432F Foliar Fungicide and other Group 3 fungicides. A gradual or total loss of pest control may occur over time if these fungicides are used repeatedly in the same fields. Other resistance mechanisms that are not linked to site of action but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance management strategies should be followed.

To delay fungicide resistance:

- Where possible, rotate the use of Folicur 432F Foliar Fungicide or other Group 3 fungicides with different groups of fungicides that control the same pathogens.
- Do not make more than one application of Folicur 432F Foliar Fungicide per year. Avoid making consecutive applications of other fungicides in the same group in a season.
- Fungicide use should be based on an IPM program that includes scouting, historical information related to pesticide use and crop rotation and considers cultural, biological and other chemical control practices.
- Monitor treated fungal populations for signs of resistance development. If disease continues to progress after treatment with this product, do not increase the use rate. Discontinue use of this product and switch to another fungicide with a different target site of action, if available.
- Contact local extension specialists or certified crop advisors for any additional pesticide resistance management and/or IPM recommendations for specific crops and disease problems in the area.

7.6 Conclusions

7.6.1 Summary

Claim for suppression of Fusarium head blight (*Fusarium* spp.) on wheat (including spring wheat, winter wheat and durum wheat) is acceptable. The claims for control of rust (leaf rust, stripe rust and stem rust), Septoria leaf blotch, tan spot and powdery mildew on wheat are also acceptable.

Confirmatory aerial application studies, to be conducted under adequate disease pressure, are required to support this application method.

Table 7.6.1 Summary of Label Proposals and Recommendations

Proposed		Recommendation (based on value assessment)	Comments
Crop/Pest	**Details**		
Wheat (spring wheat, winter wheat and durum wheat)			
Suppression of Fusarium head blight	Apply Folicur 432F Foliar Fungicide at 292 mL/ha when at least 75% of the wheat heads on the main stem are fully emerged to when 50% of the heads on the main stem are flowering.	One application per season. Folicur can be mixed with the non-ionic surfactants, Agral 90 or AgSurf.	A maximum of one application per year.
Control of rust (leaf rust, stripe rust and stem rust), Septoria leaf blotch, tan spot and powdery mildew	Apply Folicur 432F Foliar Fungicide at 292 mL/ha from the late vegetative (flag leaf fully emerged to awn emergence) stage to the end of the flowering stage.		
Aerial application		Conditionally accepted. Confirmatory studies are required.	

8.0 Toxic Substances Management Policy Considerations

During the review of technical tebuconazole and the associated end-use product, Folicur 432F Foliar Fungicide, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product does not meet the TSMP Track 1 criteria for the following reasons.

- Tebuconazole meets the criterion for persistence. The DT_{50} values in soil (770 days), water (1386 days) and sediment (no transformation) are above the TSMP Track 1 cut-off criteria for soil ($\geq$ 182 days), water ($\geq$ 182 days) and sediment ($\geq$ 365 days). Although data on the persistence in air were not available, the vapour pressure and Henry's law constant indicate that tebuconazole will not volatilize from water or moist soil under field conditions, thus long-range atmospheric transport of tebuconazole is not likely to occur.

- Tebuconazole does not meet the criterion for bioaccumulation. The log K_{ow} was 3.70, which is below the TSMP Track 1 cut-off criterion of log $K_{ow} \geq 5$. Bioconcentration factors for the edible, viscera, whole fish and earthworm were 13, 150, 78 and 1.35, respectively, which are below the TSMP Track 1 cut-off criterion of bioconcentration factors ≥ 5000.

---

[1] The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics.

[2] Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3758; e-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca.

- The toxicity of tebuconazole is summarized in Section 3.0.

- Tebuconazole does not form any major transformation products that meet the TSMP Track 1 criteria.

- Technical tebuconazole does not contain any impurities of toxicological concern as identified in Section 2.14 of DIR98-04 nor any TSMP substances as listed in Appendix II of DIR99-03.

- The end-use product, Folicur 432F Foliar Fungicide, does not contain any USEPA List 1 formulants or formulants known to be TSMP Track 1 substances. One of the formulants contains an USEPA List 2 ingredient at a maximum of 0.0072%.

Therefore, the use of Folicur 432F Foliar Fungicide, containing tebuconazole, is not expected to result in the entry of TSMP Track 1 substances into the environment.

The proposed registration of tebuconazole and Folicur 432F Foliar Fungicide is, therefore, consistent with the PMRA's strategy for implementing the TSMP.

9.0 Regulatory Decision

The active ingredient tebuconazole and its associated end-use product Folicur 432F Foliar Fungicide, which contains 432 g/L tebuconazole for the control of selected diseases caused by fungal pathogen on wheat, have been granted temporary registration under the Pest Control Products Regulations, subject to the generation of the studies listed in Section 9.2.

9.1 Label Amendments/Recommendations

9.1.1 Technical Tebuconazole

Due to the slight acute toxicity via the oral route and inhalation routes, the label for technical grade tebuconazole should have the signal words "CAUTION POISON" on the primary label display panel and "Harmful if swallowed or inhaled" on the secondary display panel. The current draft label for the technical material has the hazard statement "WARNING POISON" and "CAUTION EYE IRRITANT" on the primary display panel. These statements are not required but are acceptable.

The precautionary labelling under **ENVIRONMENTAL HAZARDS** section of the proposed label should be replaced with the following:

- **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

9.1.2 Folicur 432F Foliar Fungicide

The current draft label statements "CAUTION: EYE IRRITANT" and "DANGER: SKIN IRRITANT" are not required, but are acceptable.

Primary Label Panel
On the primary display panel of the proposed label, immediately after the statement:

- FOR THE SUPPRESSION OF *FUSARIUM* HEAD BLIGHT (SCAB) AND CONTROL OF FOLIAR DISEASES ON WHEAT

add the following statement:

- The 9.5 L jugs are intended for use by applicators who spray less than 100 hectares of wheat per day. Applicators who spray more than 100 hectares per day MUST use closed transfer equipment (i.e., XXX L totes) during mix/load activities.

Under the **PRECAUTIONS** section of the proposed label, replace:

- Wear a long-sleeved shirt and long pants, shoes plus socks, coveralls, goggles or a face shield and chemical-resistant gloves.

with:

- All workers must wear cotton/polyester coveralls over long-sleeved shirt, long pants and chemical-resistant gloves during mixing, loading, application, clean-up and repair activities. Coveralls are not required during application within closed cabs or cockpits.

Under the **DIRECTIONS FOR USE** section of the proposed label, replace:

- Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours.

with:

- Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 6 days.

Under the **DIRECTIONS FOR USE** section of the proposed label, replace:

- Applications may not be made within 30 days of harvest.

with:

- Applications may not be made within 36 days of harvest.

Under the **DIRECTIONS FOR USE** section of the proposed label, under FIELD SPRAYER APPLICATION, add the following statement:

- **DO NOT** apply during periods of dead calm or when winds are gusty. **DO NOT** apply with spray droplets smaller than the ASAE medium classification.

Under the **DIRECTIONS FOR USE** section of the proposed label, under AERIAL APPLICATION, add the following statement:

- **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the ASAE medium classification.

The generic aerial application label instructions should also be added to the label, as per Regulatory Directive DIR96-04, *Aerial Application of Pesticides*.

Under the **DIRECTIONS FOR USE** section of the proposed label, in the **MIXING** section, modify the last sentence as follows:

- Folicur 432F Foliar Fungicide is recommended for use with the registered non-ionic surfactant, Agral 90 or AgSurf at 0.125% vol/vol.

Under the **DIRECTIONS FOR USE** section of the proposed label, under the DISEASES column, modify:

- *Septoria* (Leaf Blotch and Glume Blotch)

as follows:

- *Septoria* Leaf Blotch

Under the **DIRECTIONS FOR USE** section of the proposed label, in the REMARKS column, modify the 5th paragraph as follows:

- A maximum of one application of FOLICUR 432F Foliar **FUNGICIDE** may be applied per crop season.

When a tank mixture is used, consult the labels of the tank mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

Under the **ENVIRONMENTAL HAZARDS** section of the proposed label, replace the existing statements with the following:

- Tebuconazole is persistent and will carryover. It is recommended that any products containing tebuconazole not be used in areas treated with this product during the previous season, i.e., this product should be used only in alternate years.

  Toxic to birds, small wild mammals, aquatic organisms and non-target plants. **DO NOT** apply directly to water or to areas where surface water is present or to intertidal areas below the mean high water mark. Runoff is hazardous to aquatic organisms in neighbouring areas. **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes. To reduce the run off refer to the recommendation under "APPLICATION IN FIELDS ADJACENT TO AQUATIC AREAS".

Application in Fields Adjacent to Aquatic Areas

Under the **APPLICATION IN FIELDS ADJACENT TO AQUATIC AREAS** section of the proposed label, add the following:

- **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

- To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to, heavy rainfall, moderate to steep slope, bare soil, poorly drained soil (e.g., soils that are compacted or fine textured). Avoid application of this product when heavy rain is forecast.

Spray Drift Management for Aerial and Ground Applications

Under **SPRAY DRIFT MANAGEMENT FOR AERIAL AND GROUND APPLICATIONS** section of the proposed label, under the title "WIND", change the wind speed to "greater than 16 km/h".

Resistance Management

Add the following statements in a new section of the label entitled **RESISTANCE MANAGEMENT RECOMMENDATIONS**:

- For resistance management, please note that Folicur 432F Foliar Fungicide contains a Group 3 fungicide. Any fungal population may contain individuals naturally resistant to Folicur 432F Foliar Fungicide and other Group 3 fungicides. A gradual or total loss of pest control may occur over time if these fungicides are used repeatedly in the same fields. Other resistance mechanisms that are not linked to site of action but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance management strategies should be followed.

- **To delay fungicide resistance,**
  Where possible, rotate the use of Folicur 432F Foliar Fungicide or other Group 3 fungicides with different groups of fungicides that control the same pathogens.

  Do not make more than one application of Folicur 432F Foliar Fungicide per year. Avoid make consecutive applications of other fungicides in the same group in a season.

  Fungicide use should be based on an integrated pest management (IPM) program that includes scouting, historical information related to pesticide use and crop rotation and considers cultural, biological and other chemical control practices.

Monitor treated fungal populations for sign of resistance development. If disease continues to progress after treatment with this product, do not increase the use rate. Discontinue use of this product and switch to another fungicide with a different target site of action, if available.

Contact your local extension specialist or certified crop advisors for any additional pesticide resistance-management and/or IPM recommendations for specific crops and disease problems in your area.

9.2 Additional Data Requirements

DACO 7.4.1 **Supervised residue trial study**

The number and location of the supervised residue trials submitted on wheat are insufficient to meet the guideline requirements set out in Section 9 of Regulatory Directive DIR98-02. Therefore, additional magnitude of the residue data are required from supervised residue trial on wheat in order to fulfill the guideline requirements. Eleven supervised crop field trials on wheat are to be carried out at GAP, i.e., one application of Folicur 432F Foliar Fungicide at the proposed maximal seasonal application rate of 126 g a.i./ha with a PHI of 36 days, in the Canadian representative regions of Zone 7 (3 trials), Zone 7A (1 trial), and Zone 14 (7 trials). In accordance with Section 9 of Regulatory Directive DIR98-02, the number of supervised crop field trials on wheat can be reduced by 25% if the residue profile consistently shows a pattern of less than the LOQ. Under this condition, the number of supervised crop field trial on wheat can be reduced from 11 to 6, with 1 trial conducted in Zone 7; 1 trial, in 7A; and 4 trials, in Zone 14.

DACO 7.4.2	**Residue decline study** The residue decline studies submitted on wheat lack information on the behaviour of tebuconazole residues in/on wheat at and before the PHI of 36 days. Therefore, in accordance with Section 9 of Regulatory Directive DIR98-02, decline data on the magnitude of the residue of tebuconazole in/on wheat harvested at PHI of 36 days ± 7 and 14 days, i.e., at PHI of 22, 29, 36, 43 and 50 days, are required. The data are to be generated from two sites in the applicable Canadian representative regions for wheat, i.e., Zone 5, 7, 7A or 14, in accordance with Section 9 of Regulatory Directive DIR98-02.
DACO 8.3.2.1	**Canadian field dissipation study** The applicant is conducting a multiyear field study with anticipated completion in December 2004
DACO 9.3.4	**Chronic toxicity study of tebuconazole to a sediment-dwelling aquatic organisms**
DACO 9.5.2.4	**Acute study on marine/estuarine fish**
DACO 9.6.3.1	**Study on chronic/reproductive effects in bobwhite quail**
DACO 9.8.4	**Seedling emergence toxicity study on vascular plant (Tier 2)**
DACO 10.2.3.3	**Small-scale trials (field, greenhouse)** Two confirmatory aerial studies are required. The studies must be conducted under adequate disease pressure.

Two studies were submitted to support aerial application. Both studies were conducted under low disease pressure. Confirmatory aerial studies conducted under adequate disease pressure are required.

List of Abbreviations

µg	microgram
µL	microlitre
AD	administered dose
ADI	acceptable daily intake
a.i.	active ingredient
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
AST	aspartate aminotransferase
BBCH	BASF, Bayer, Ciba-Geigy and Hoechst
bw	body weight
bwg	body-weight gain
BWI	body weight per individual
cm	centimetre
DACO	data code
DCM	dichloromethane
DEEM	Dietary Exposure Evaluation Model
DFR	dislodgeable foliar residue
DI	daily intake
DON	deoxynivalenol
DT_{50}	dissipation time 50%
EC_{25}	effect concentration to 25%
EC_{50}	effect concentration to 50%
ECW 4390	hydroxy tebuconazole sulfate
ECW 4393	hydroxy tebuconazole glucuronide
EEC	expected environmental concentration
EPPO	European and Mediterranean Plant Protection Organization
EXAMS	Exposure Analysis Modeling System
F	female
F_0	parental animals
F_1	1st generation offspring
FDK	*Fusarium* damaged kernel
FHB	*Fusarium* head blight
g	gram
GAP	good agricultural practice
GC	gas chromatography
GC-FID	gas chromatography using a flame ionisation detector
GC-NPD	gas chromatography using a nitrogen detector
GD	gavage dose
h	hour(s)
ha	hectare
Hb	hemoglobin
Hct	hematocrit

HPLC	high performance liquid chromatography
HWG 1608	tebuconazole
HWG 2061	hydroxy tebuconazole
HWG 2443	tebuconazole acid
IPM	integrated pest management
kg	kilogram
K_{oc}	adsorption quotient normalized to organic carbon
K_{ow}	*n*-octanol–water partition coefficient
K_d	adsorption coefficient
L	litre
LADD	lifetime average daily dose
LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LEACHM	Leaching Estimation and Chemistry Model
LOAEL	lowest observed adverse effect level
LOD	limit of detection
M	male
m	metre
MAS	maximum average score
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre
MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue limit
MRM	multiresidue method
MTD	maximum tolerated dose
MTDB	maximum theoretical dietary burden
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NT	not tested
NZW	New Zealand white
PHI	preharvest interval
OECD	Organisation for Economic Cooperation and Development
OPPTS	Office of Prevention, Pesticides and Toxic Substances
p	probability
PAM	*Pesticide Analytical Manual*
PCP	pest control product
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
ppm	parts per million
PRZM	Pesticide Root Zone Model
Q^{1*}	cancer risk value
RAC	raw agricultural commodity

Rf	retention time value
ROC	residue of concern
RQ	risk quotients
SD	standard deviation
TLC	thin layer chromatography
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
UV	ultraviolet

Appendix I Toxicology

Table 1 Summary Table

** Denotes studies previously submitted and reviewed.

METABOLISM

Study no. 1 – Wistar rats received either a single oral low dose (2 mg/kg bw), a repeat oral low dose (2 mg/kg bw/day for 14 days followed by a single oral gavage dose of 2 mg/kg bw), or a single oral high dose (20 mg/kg bw) of [phenyl-UL-^{14}C]-tebuconazole.

Study no. 2 – Wistar rats received either a single oral low dose (2 mg/kg bw of [phenyl-UL-^{14}C]-label), a repeat oral low dose (2 mg/kg bw/day [non-labelled] for 14 days followed by a single oral gavage dose of 2 mg/kg bw [phenyl-UL-^{14}C]-label), or a single oral high dose (20 mg/kg bw) of [triazole-3, 5-^{14}C]-tebuconazole.

Rate and extent of absorption and excretion:
Study no. 1 – Plasma concentrations peaked quickly indication rapid absorption of tebuconazole. Plasma levels peaked more quickly in females (0.33–0.67h) than males (1.0–1.5h). The half-lives were similar for both sexes (31.9–52.2h). Excretion occurred mainly via the feces (79.0% in males, 62.2% in females) and the urine (16.1% in males, 31.3% in females) within 48–72h. Excretion by respiration accounted for 0.03% of the administered dose. Absorption and excretion were not dependent on dose or pretreatment for 14 days.

Study no. 2 – Within 48–72h more than 90% of the phenyl-labelled tebuconazole was excreted via the feces (77.1–80.3% in males, 60.6–67.5% in females) and the urine (14.5–16.8% in males, 24.1–33.6% in females). There were no sex differences in fecal or urinary excretion patterns for the triazole-labelled tebuconazole. By 48–72h, the phenyl-labelled compound was almost completely metabolized, while the triazole-labelled compound was completely metabolized by both males and females. Absorption and excretion were not dependent on dose or pretreatment for 14 days.

Distribution / target organ(s):
Study no. 1 – The overall distribution of labelled-tebuconazole was low in the organs and tissues, but higher in males (0.6%) than females (0.3%). The liver and kidney contained the highest amounts, the lowest amount was found in the brain and bones, in both sexes.

Toxicologically significant compound(s):
Study no. 2 – The parent molecule was metabolized to give an alcohol (HWG 2061, 18.3–26.3%) and an acid (HWG 2443, 24.2–24.7%) which were excreted in the feces. HWG 2061 was further conjugated to a sulfate metabolite (HWG 2061-sulfate, 0.1–2.3%) and a glucuronide (HWG 2061-glucuronide, 0.3–4.1%) which were excreted in the urine. The alcohol metabolite HWG 2061 was also converted to a triol (ECW 4886, 0.5–3.2%) found in the feces and was additionally excreted in the urine as a glucuronide conjugate (ECW 4886-glucuronide, 1.1%). The acid metabolite HWG 2443 was also converted to a keto-acid (ECW 4881/ECW 4873) found in the feces (0.1–1.8%) and urine (1.0–2.2%). Two minor metabolites were also found in the feces after undergoing changes on the phenyl ring (ECW 4882, 3.7–4.0% and ECW 2251, 0.6–0.9%). The triazole ring was cleaved off the parent molecule to yield another minor metabolite excreted in the urine (1.5–5.4%).

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
ACUTE STUDIES—TECHNICAL [Tebuconazole]			
Oral HWG 1608 purity: 98.0% a.i.	Rat—Sprague Dawley (5/sex) ♂, ♀: 1600, 2300, 3000, 3900 or 5000 mg/kg bw ♀: 730, 950 or 1230 mg/kg bw	♂: LD_{50} = 4000 mg/kg bw **♀: LD_{50} = 1700 mg/kg bw** Combined: LD_{50} = 2850 mg/kg bw	**Slight acute toxicity** Mortalities at 3000–5000 mg/kg bw (♂), 950–2300 mg/kg bw (♀). At 2300–5000 mg/kg bw, sedation, abnormal gait and emaciation resolved day 5 onward. At necropsy, liver discolouration and testicular atrophy. Animals necropsied during study following death showed liver hypertrophy and marked lobular pattern. **"CAUTION POISON"** "Harmful if swallowed"
Oral HWG 1608 Purity: 98.0% a.i.	Mouse—ICR Crj:CD-1 (5/sex) ♂, ♀: 3000, 3900 or 5000 mg/kg bw ♂: 1600 or 2300 mg/kg bw	**♂: LD_{50} = 2800 mg/kg bw** ♀: LD_{50} = 5200 mg/kg bw Combined: LD_{50} = 4000 mg/kg bw	**Low acute toxicity** Mortalities at 3900–5000 mg/kg bw (♂,♀)) and 1600–3000 mg/kg bw (♂). At 2300–5000 mg/kg bw, sedation, abnormal gait and emaciation, resolved day 2 onward. Abnormal findings in liver (♂: discolouration) and gastronintestinal tract (♂,♀): discolouration, redness) during necropsy.
Dermal	Rat—Wistar (5/sex) 5000 mg/kg bw (single dose)	LD_{50} > 5000 mg/kg bw	**Low acute toxicity** No mortalities. No treatment related effects during study or at necropsy.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Inhalation (nose and head)	Rat—Wistar (5/sex) 0.371 mg/L aerosol 5.093 mg/L dust	LC_{50} aerosol > 0.371 mg/L LC_{50} dust > 5.093 mg/L	**Low acute toxicity*** No mortalities. No treatment related effects during study, isolated foci in lungs noted in 1 aerosol-treated ♂ and 1 dust-treated ♂ during necropsy. *highest nominal conc. of 4.0 mg/L vs. highest actual conc. of 0.371 mg/L, limited by highest achievable aerosol conc. Although LC_{50} of 0.371 requires a *WARNING* statement, lack of clinical signs indicate low toxicity via this route. Recommend "**CAUTION POISON**" "Harmful if inhaled"
Skin irritation	Rabbit—NZW (3/sex) 500 mg undiluted test material	MIS = 0 MAS (24,48,72 h) = 0	**Non-irritating** No mortalities or clinical signs.
Eye irritation	Rabbit—NZW (3/sex) 100 mg undiluted test material	MIS = 9.7/110 at 1 h MAS (24, 48, 72 h) = 3.7/110	**Minimally irritating** Mild to moderate conjunctival redness, chemosis and discharge in all animals after 1 h, resolved by 72 h to day 8.
Skin sensitization (Buehler)	Guinea Pig—Hartley (15 ♂ test group, 5 ♂ control group) **Induction:** 100% (undiluted) 0.4g test material **Challenge:** 100% (undiluted) 0.4g test material	Negative	**Not a skin sensitizer**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Isomer and metabolite studies			
Intra peritoneal HWG 1608 Symmetric isomer purity: 98.6% a.i.	Rat—Sprague Dawley (5/group, ♀ only) 100, 500, 800, 1000 or 1400 mg/kg bw	LD_{50} = 1100 mg/kg bw	Mortalities at 800–1400 mg/kg bw. ↑Urine discharge, lying on the side, poor reflexes, red-stained bedding, reduced motility/spastic gait (> 1000 mg/kg), resolved starting day 6 onward. Abnormal findings (white deposits, swelling, discolouration) in liver, fat tissue, pancreas and abdominal wall, fluid in the lungs, discoloured urine in the bladder during necropsy.
Oral HWG 2443 Metabolite purity: 99.7% a.i.	Rat—Sprague Dawley (5/group, ♀ only) 4000 mg/kg bw (single dose)	LD_{50} > 4000 mg/kg bw	**Low acute toxicity** No mortalities. Red nasal stain in 1 animal from days 0–1. No treatment related effects at necropsy.
Oral HWG 2061 Metabolite purity: 96.4% a.i.	Rat—Sprague Dawley (5/group, ♀ only) 5000 mg/kg bw (limit dose)	LD_{50} > 5000 mg/kg bw	**Low acute toxicity** No mortalities. Red nasal/oral stain and urine-stained fur in 4/5 animals from days 3–5. Diarrhea, perianal staining in 1 animal from day 0–1. No treatment related effects at necropsy.
ACUTE STUDIES—FORMULATION [Folicur 432F Foliar Fungicide–40.6% TEU]			
Oral	Rat—Sprague Dawley (5/sex) 2000, 3500 or 5000 mg/kg bw	♂: LD_{50} = 3776 mg/kg bw ♀: LD_{50} = 3710 mg/kg bw Combined: LD_{50} = 3743 mg/kg bw	**Low acute toxicity** Mortalities at 3500 and 5000 on days 1–7 (♂,♀)). Ataxia, ↓ activity, lateral/ventral recumbency and staining (head, forelimb, ventrum) were observed on days 0–3. Convulsions, tremors and ↑ reactivity noted only in animals that died by day 7. Signs were resolved by day 10 in surviving animals. Necropsy of animals found dead showed salivation, lacrimation, reddened lungs, nasal staining, ventral urine staining and abdominal fluid. One animal at scheduled sacrifice had ventral alopecia.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Dermal	Rat—Sprague Dawley (5/sex) 2011 mg/kg bw (limit dose)	LD_{50} > 2011 mg/kg bw	**Low acute toxicity** No mortalities. Muscle fasciculations, tremors, salivation, oral/lacrimal/nasal staining and urine/perianal staining were observed on day 0, resolved by day 1. No treatment related lesions observed at necropsy.
Inhalation (nose only)	Rat—Sprague Dawley (6/sex) 2.51 mg/L	LC_{50} > 2.51 mg/L	**Low acute toxicity** No mortalities. Lack of grooming, urine stains, red lacrimation and nasal stains noted in ♀, resolved by day 6. One ♀ at scheduled sacrifice had minimal ventral alopecia.
Skin irritation	Rabbit—NZW (6 ♂) 0.5 mL undiluted test material	MIS = 1/8 MAS (24, 48, 72 h) = 0	**Slightly irritating** No mortalities. Mild erythema observed in 5/6 rabbits within 1 hour of dosing, resolved by 24 hours. No label statements required.
Eye irritation	Rabbit—NZW (6 ♂) 0.1 mL undiluted test material	MIS = 5.7/110 at 1 h MAS (24, 48, 72 h) = 2.1/110	**Minimally irritating** No mortalities. Mild conjunctival redness and chemosis noted in all animals 1hour after dosing, and mild to moderate conjunctival discharge noted in 3 animals at 1 hour. All signs of irritation resolved by day 7.
Skin sensitization (Buehler)	Guinea pig—Hartley (15 ♂ test group, 5 ♂ control group) **Induction:** 100% (undiluted) 0.4mL test material **Challenge:** 100% (undiluted) 0.4mL test material	Negative	**Not a skin sensitizer**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
SHORT-TERM TOXICITY			
21-day inhalation Rat	Bor:WISW Spf-cpb (10/sex/dose, 6 h per day / 5 days per week) 0, 0.0012, 0.0106 or 0.1558 mg/L/day ***approximately** equivalent to 0, 0.326, 2.88 or 42.3 mg/kg bw/day (calculated by reviewer)	NOAEL = 0.1558 mg/L/day (42.3 mg/kg bw/day)	**0.1558 mg/L/day**: ↑ liver N-demethylase activity and piloerection observed day 9–21. Not considered adverse.
**21-day dermal Rabbit	NZW (3/sex/dose) for unabraded and abraded groups 0, 50 or 250 mg/kg bw/day, 6 hours per day, 5 days per week	NOAEL > 250 mg/kg bw/day	No adverse treatment related findings.
**21-day dermal Rabbit	NZW (5/sex/dose) 0 or 1000 mg/kg bw/day, 5 days per week	NOAEL = 1000 mg/kg bw/day	Slight thickening and redness of skin at application site. Slightly ↑ of liver weights, no accompanying histopathological changes.
28-day dietary Mouse	NMRI (5/sex/dose) 0, 125, 500 or 2000 ppm **♂:** 0, 12.6, 47.0 or 181.7 mg/kg bw/day, ♀: 0, 14.1, 53.2 or 236.0 mg/kg bw/day)	No NOAEL was established–range-finding study.	**125 ppm:** Lipid accumulation observed in hepatocyte plasma (2/10 animals), ↑ relative liver weight (♀). Pathology included one ♂ with enlarged spleen. **500 ppm:** ↓ bwg (♂/♀), ↑ liver enzymes ALP (♂), AST (♀), ALT (♀), ↓ cholesterol (♀), ↑ absolute and relative liver weight (♀) **2000 ppm:** ↓ bwg (♂/♀), ↓ food consumption (♂), ↑ liver enzymes ALP (♂), AST (♂), ↑ absolute and relative liver weight (♂/♀)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
**28-day dietary Rat	Bor:WISW Spf-cpb (20/sex/dose) 0, 30, 100 or 300 mg/kg bw/day followed by 28 day recovery period for 10 rats/sex/dose	NOAEL = 30 mg/kg bw/day LOAEL = 100 mg/kg bw/day	**100 mg/kg bw/day:** ↓ Hb and Hct, ↑ liver weight (♂,♀), ↑ liver enzymes (N-, O-demethylases) (♂), ↑ spleen weight (♀) **300mg/kg bw/day:** ↓ bwg, ↓ Hb and Hct, ↑ liver weight , ↑ liver enzymes (N-DEM, O-DEM and P450). Histopathologic changes noted in liver (enlarged and fatty (♂), bile duct proliferation and ↑ mitosis (♀); spleen (↓ iron pigment, ↑ connective tissue, atrophied follicles); adrenals (enlarged zona glomerulosa, fat vacuoles and large sinusoial cells); lungs (proliferation, honeycomb structure) and bone marrow (fat cells present, ↓ hematopoeisis. ↑ AST, ALT, ALP and spleen weight (♀). One ♀ died (also one control ♀ died). All changes reversed during recovery except for histopathological liver/spleen effects in ♀.
**90-day dietary Rat	Bor:WISW Spf-cpb (10/sex/dose) 0, 100, 400 or 1600 ppm ♂: 0, 7.5, 34.8 or 171.7 mg/kg bw/day ♀: 0, 9.4, 46.5 or 235.2 mg/kg bw/day	NOAEL = 100 ppm (♂ = 7.5 mg/kg bw/day, ♀ = 9.4 mg/kg bw/day) LOAEL = 400 ppm (♂ = 34.8 mg/kg bw/day, ♀ = 46.5 mg/kg bw/day)	**400 ppm:** ↓ absolute liver weight (♂), ↑ vacuole formation in adrenals (♀) **1600 ppm:** Two deaths (1 ♂, 1 ♀), ↓ bw, ↓ plasma triglycerides (♂), ↓ absolute liver weight, ↑ N-DEM and P450 (♂),↑ relative liver weight (♀), ↑ vacuole formation in adrenals (♀), ↑ hemosiderin accumulation in spleen (♀)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
**90-day dietary Dog	Beagle (4/sex/dose) 0, 200, 1000 or 5000 ppm ♂: 0, 7.2, 37.6 or 214.8 mg/kg bw/day ♀: 0, 7.7, 36.3 or 226.6 mg/kg bw/day	NOAEL = 200 ppm (♂ = 7.2 mg/kg bw/day, ♀ = 7.7 mg/kg bw/day) LOAEL = 1000 ppm (♂ = 37.6 mg/kg bw/day, ♀ = 36.3 mg/kg bw/day)	**1000 ppm:** thin appearance (2 ♂), ↓ bwg in ♂/♀, ↓ food consumption (♀), ↑ N-demethylase activity **5000 ppm:** One death (♂) on day 2. ↑ ALP, ↑ spleen weight, severe anisocytosis (6/8 animals). Cataracts and lens degeneration were observed in all high dose animals, liver (Kupfer cells) and spleen (siderocytes) contained ↑ hemosiderin pigments, and ↑ adrenal cell vacuolation was observed.
**12-month dietary Dog	Beagle (4/sex/dose) 0, 40, 200 or 1000 (weeks 1–39) /2000 (weeks 40–52) ppm ♂: 0, 1.05, 6.43 or 39.8 mg/kg bw/day ♀: 0, 1.05, 6.4 or 43.0 mg/kg bw/day	NOAEL = 40 ppm (♂/♀ = 1.05mg/kg bw/day) LOAEL = 200 ppm (♂/♀ = 6.4 mg/kg bw/day	**200 ppm:** 2 ♀ with vacuoles in adrenal zona fasciculata–moderate to severe (not considered adverse). Lens alteration noted in two animals with no impairment of vision. **1000/2000 ppm:** ↑ hemosiderin accumulation in spleen, ↑ N-DEM activity in liver, ↑ triglycerides in liver, liver lobulation observed in both sexes. 2 ♀ with vacuoles in adrenal zona fasciculata–slight to moderate (not considered adverse). Lens alteration noted in one animal with no impairment of vision.
**12-month dietary Dog	Beagle (4/sex/dose) 0, 100 or 150 ppm 0, 2.96 and 4.39 mg/kg bw/day	NOAEL = 100 ppm (♂/♀ = 2.96 mg/kg bw/day) ***ADI based on this NOAEL*** LOAEL = 150 ppm (♂/♀ = 4.39 mg/kg bw/day)	**150 ppm:** Hypertrophy of adrenal zona fasciculata (in all 8 high dose animals, 1 control animal), fatty vacuoles in adrenal zona glomerulosa cells (3 ♂, 1 ♀ in high dose group, 1 ♂ and 1 ♀ in control group). Severity of effect was minimal to mild in control and treated groups.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
CHRONIC TOXICITY AND ONCOGENICITY			
**21-month dietary Mouse	NMRI, 50/sex/dose for 21 months (main group) and 10/sex/dose treated for 12 months (interim group) 0, 20, 60 or 180 ppm ♂: 0, 5.9, 18.2 or 53.1 mg/kg bw/day ♀: 0, 9.0, 26.1 or 80.5 mg/kg bw/day	NOAEL = 60 ppm (♂ = 18.2 mg/kg bw/day, ♀ = 26.1 mg/kg bw/day) LOAEL = 180 ppm (♂ = 53.1 mg/kg bw/day, ♀ = 80.5 mg/kg bw/day)	**≤ 60 ppm:** In ♀, ↑ plasma bilirubin (no accompanying liver lesions—was not considered adverse), periportal vacuolation was observed (40% vs. 0% in control) at 12 months only. No effects observed in ♂ at this dose. **180 ppm:** In ♀, ↑ plasma bilirubin at 12 and 21 months, periportal vacuolation was observed at 12 months (50%) but not at 21 months (with non-significant increase in absolute and relative liver weight at 12 and 21 months). In ♂, significant ↑ in relative liver weight at 21 months, 40% ↑ periportal vacuolation at 12 months, 16% ↑ periportal vacuolation at 21 months, 16% centrilobular fine vacuolation at 21 months. Vacuoles were attributed to lipid deposition in the liver. No ↑ tumor incidence; however, reviewer concluded that the **MTD was not reached** in this study.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
**21-month dietary Mouse	NMRI, 50/sex/dose (main group) and 10/sex/dose treated for 12 months (interim group) 0, 500 or 1500 ppm ♂: 0, 84.9 or 279.0 mg/kg bw/day ♀: 0, 103.1 or 356.5 mg/kg bw/day	No NOAEL for systemic effects was established. LOAEL systemic = 500 ppm NOAEL carcinogenicity = 500 ppm (♂ = 84.9 mg/kg bw/day, ♀ = 103.1 mg/kg bw/day) LOAEL carcinogenicity = 1500 ppm (♂ = 279.0 mg/kg bw/day, ♀ = 356.5 mg/kg bw/day)	**≥ 500 ppm:** Significant, dose related ↑ in liver weight and ALT activity. **1500 ppm:** bw (♂) was significantly lower than controls (> 10%), in ♀ bw was < 10% lower than control. Significant ↑ in hepatic ALT and ALP activity, ↑ incidence of non-neoplastic and neoplastic lesions such as focal hyperplasia of hepatocytes, panacinar fine fatty vacuolation, oval cell proliferation, **hepatocellular adenoma** (17/48 ♂ vs. 0/47 in controls; 2/46 ♀ vs. 0/47 in controls), and **hepatocellular carcinoma** (10/48 ♂ vs. 1/47 in controls; 12/46 ♀ vs. 3/47 in controls). Author's conclusion: Severe liver damage indicated that MTD was exceeded. The PMRA concluded after re-evaluating this study that the MTD was not exceeded. There is evidence to indicate the carcinogenic potential of tebuconazole at the highest dose level of 1500 ppm (hepatocellular carcinomas and adenomas in ♀ and ♂). Under the conditions of this study, tebuconazole was considered carcinogenic in mice.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
**2-year dietary Rat	Wistar (Bor:WISW Spf Cpb) 50/sex/dose for 2 years (main group) and 10/sex/dose for 1 year (satellite group) 0, 100, 300 or 1000 ppm ♂: 0, 4.7, 15.9 or 55 mg/kg bw/day ♀: 0, 6.5, 22.8 or 86.3 mg/kg bw/day	NOAEL = 100 ppm (♂ = 4.7 mg/kg bw/day, ♀= 6.5 mg/kg bw/day) LOAEL = 300 ppm (♂ = 15.9 mg/kg bw/day, ♀ = 22.8 mg/kg bw/day)	**300 ppm:** Significant ↓ in bw and adrenal weights (♀ only). No change in food consumption. **1000 ppm:** In ♀, a significant ↑ in hemosiderin content in the spleen, ↓ hemorrhagic cortical degeneration in the adrenals and liver enzyme induction (a non-significant ↑ in hepatic hemosiderin content was also noted). No ↑ in neoplastic lesions at 1 year. After 2 years, a slight ↑ (not significant) in thyroid C-cell adenoma and carcinoma (combined) was observed (for 0, 100, 300 or 1000 ppm incidence was 0/49, 2/49, 3/50 or 3/50) in ♂ only. Results were in the range of historical control data. Incidence of c-cell hyperplasia (for 0, 100, 300 or 1000 ppm) was 1/49, 3/49, 7/50 and 6/50. No evidence of carcinogenicity in the rat.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
**Multi-generation dietary Rat	25 Wistar (Bor:WISW Spf Cpb) rats/sex/dose 0, 100, 300 or 1000 ppm ♂: 0, 7.2, 24.4 or 84.8mg/kg bw/day* ♀: 0, 8.9, 30.9 or 103.1 mg/kg bw/day* *Average intake by ♂/♀ for both F_0 and F_1 generations during premating phase only F_0 parents were mated 3 times to give F_{1a}, F_{1b} and F_{1c} litters. F_{1b} rats were fed to treated diets to maturity and mated twice to give F_{2a} and F_{2b} litters. F_{1c} litter was sacrificed at birth.	NOAEL = 300 ppm (♂ = 24.4 mg/kg bw/day, ♀ = 30.9 mg/kg bw/day) LOAEL = 1000 ppm (♂ = 84.8mg/kg bw/day, ♀ = 103.1 mg/kg bw/day)	**1000 ppm:** One death (♀). ↓ bwg of F_0 and F_{1b} parents during the period of 2 gestations/generation (no change in food consumption), ↓ viability and lactation index in 2 litters of F_0 parents, ↓ pup birth weight in 1st litter of F_0 parents and both litters of F_{1b} parents, ↓ pup body weight during lactation in both litters of both generations. No gross or histopathological changes noted. Not separated into parental vs pup effects. ↓ viability in F_1 generation may indicate a slight ↑ in qualitative sensitivity of the young.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
**Developmental toxicity Rat	Wistar, 25/dose 0, 23, 47.5 or 99.8 mg/kg bw/day by gavage; GD 6–15	Maternal systemic effects NOAEL = 23 mg/kg bw/day LOAEL = 47.5 mg/kg bw/day Developmental effects NOAEL = 47.5 mg/kg bw/day LOAEL = 99.8 mg/kg bw/day	**Maternal systemic effects** **≥ 47.5 mg/kg bw/day:** ↓ bwg GD6–11, ↓ food consumption GD 6–16, ↑ absolute and relative liver weight **Developmental effects** **99.8 mg/kg bw/day:** ↑ embryonic and fetal resorptions, ↓ no. of live fetuses, ↓ fetal bw. 2/232 fetuses in separate litters with malformation (one with agnathia, microstoma and anopthalmia, 2nd with no tail). Incidence was considered to be within range of historical control data for spontaneous malformations. ↑ visceral/skeletal findings: fluid in thoracic cavity (4/116 fetuses in 2/24 litters vs. 0/144 fetuses in 0/24 litters in control), bipartite/dumbell-shaped thoracic vertebral centra (8/116 fetuses in 5/24 litters vs. 2/144 fetuses in 2/24 litters in control). Not considered a teratogen in rats.
** Developmental toxicity Mouse	25 NMRI mice/dose 0, 8.6, 30 or 84 mg/kg bw/day by gavage, GD 6–15	Maternal systemic effects NOAEL = 84 mg/kg bw/day Developmental effects NOAEL = 8.6 mg/kg bw/day LOAEL = 30 mg/kg bw/day	**Maternal systemic effects** No maternal toxicity was observed at any dose level. **Developmental effects** **> 30 mg/kg bw/day:** Fetotoxicity, ↑ number of runts. **84 mg/kg bw/day:** ↑ number of runts, ↑ placental weights, significant ↑ in malformations (13/60 fetuses in 8 litters vs. 1/68 fetuses in 1 control litter), including cleft palate (6/60 fetuses in 4 litters compared to 1/68 fetuses in 1 concurrent control litter). Indicative of teratogenicity at non-maternally toxic doses.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental toxicity Mouse	NMRI mice, 35/dose in main study (10/dose for hematology and biochemistry), 30/dose in supplemental study **Main study:** 0, 10, 30 or 100 mg/kg bw/day by gavage; GD 6–18 **Supplemental study:** 0, 1 and 3 mg/kg bw/day by gavage; GD 6–18	Maternal systemic effects NOAEL = 10 mg/kg bw/day LOAEL = 30 mg/kg bw/day Developmental effects NOAEL = 3 mg/kg bw/day LOAEL = 10 mg/kg bw/day	**Maternal systemic effects** **10 mg/kg bw/day:** liver enzyme (P450, O-DEM) induction, mild liver vacuolization in dams in the hematology/biochemistry subgroup only (10/dose in this group). Not considered adverse. **30 mg/kg bw/day:** ↑ postimplantation loss, ↑ liver triglycerides, ↑ liver weight, ↑ ALP activity, mild liver vacuolization **100 mg/kg bw/day:** ↑ liver and spleen relative weight, ↑ liver triglycerides, ↑ liver enzyme (P450, O-DEM) activity, moderate liver vacuolization **Developmental effects** **3 mg/kg bw/day:** Incidences of malformations within historical control range -cleft palate (1/186 fetuses), curled/kinked tails (2/186 fetuses). Skeletal variations observed in 9/99 fetuses. **10 mg/kg bw/day:** ↑ external and visceral malformations—exencephaly, wart-like growths, open eye, cleft palate, immature fetus, tail abnormalities and protruding tongue, palatal fissures, dilatation of the cerebellum, acrania and missing eye, incidence of skeletal variations and delayed ossifications was ↑ than control and mid-dose groups and equivalent to high dose group. **30 mg/kg bw/day:** ↑ postimplantation loss, ↑ external malformations— wartlike growths, exencephaly, open eye, cleft palate, protruding tongue, runt **100 mg/kg bw/day:** ↑ postimplantation loss, ↓ live

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
**Developmental toxicity Rabbit	Chinchilla, 16/dose 0, 8.5, 25.8 or 100 mg/kg bw/day by gavage; GD 6–18	Maternal systemic effects NOAEL = 25.8 mg/kg bw/day LOAEL = 100 mg/kg bw/day Developmental effects NOAEL = 25.8 mg/kg bw/day LOAEL = 100 mg/kg bw/day	**Maternal systemic effects** **100 mg/kg bw/day:** ↓ bwg during treatment **Developmental effects** **100 mg/kg bw/day:** ↑ postimplantation loss, ↑ (6.7%) in skeletal malformations (6/90 fetuses in 4/16 litters compared to 0/111 fetuses in controls). Malformations included: peromelia (5 fetuses), agenesis of hindlimb claws with an enlarged fontanelle (1 fetus), palatoschisis (1 fetus) and perodactylia (1 fetus). **Indicative of teratogenic potential.**
Developmental toxicity (1995) Rabbit	Chinchilla, 16/dose 0, 10, 30 or 100 mg/kg bw/day by gavage; GD 6–18	Maternal systemic effects NOAEL = 30 mg/kg bw/day LOAEL = 100 mg/kg bw/day Developmental effects NOAEL = 10 mg/kg bw/day LOAEL = 30 mg/kg bw/day	**Maternal systemic effects** **100 mg/kg bw/day:** ↓ food consumption (29%) during treatment, slight/minimal sinusoidal granulocytosis of the liver at 30 (3/5) and 100 (2/5) mg/kg, 1/5 at mid-dose with liver necrosis, but no D-R (histopathology performed on 5 rabbits/group only—no similar liver findings noted in subsequent mechanistic study at 100 mg/kg bw/d that examined more animals). **Developmental effects** **100 and 30 mg/kg bw/day:** ↑ incidence (5 fetuses/5 litters) of spina bifida, meningocele, omphalocele, malpositioning of limbs, acephaly, skull indentation, hypodactyly, brachydactyly and incomplete/non-ossification. **100 mg/kg bw/day:** ↑ postimplantation loss, ↓ pre-implantation loss, ↓ mean fetal weight. **Indicative of teratogenic potential and ↑ fetal sensitivity.**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental toxicity Mechanistic study (1999) (Non-guideline, supplementary) Rabbit	Chinchilla, 14–15/dose 0 and 100 mg/kg bw/day by gavage; GD 6–19	NOAEL was not determined. LOAEL = 100 mg/kg bw/day	**Maternal systemic effects** **100 mg/kg bw/day:** ↓ bwg during treatment, ↓ food consumption, adrenal hypertrophy, ↑ absolute and relative adrenal weight, ↑ corticosterone and 11-deoxycorticosterone in adrenals, 11β-hydroxylation of 11-deoxycorticosterone in adrenal mitochondria; 2/13 centrilobular cytoplasmic change of the liver **Developmental effects** **100 mg/kg bw/day:** ↓ fetal weight. No external findings (skeletal/visceral examinations not performed). Potential mechanism for developmental toxicity in rabbits—adrenal hypertrophy. **Supplemental**
**Develop-mental toxicity Mouse–dermal	NMRI–HAN, 25–27/dose (main study), 40/dose (supplementary study for histopathology) **Dermal application** of 0, 90, 275 or 780 mg/kg bw/day in 4% methyl cellulose; 6 hour/day GD 6–15	Maternal systemic effects NOAEL = 90 mg/kg bw/day LOAEL = 275 mg/kg bw/day Maternal dermal effects 780 mg/kg bw/day Developmental effects NOAEL = 275 mg/kg bw/day	**Maternal systemic effects** **275 and 780 mg/kg bw/day:** No mortalities. Fatty accumulation in hepatocytes, ↑ hepatic P450, N-demethylase and O-demethylase activities were observed. Not considered adverse. **780 mg/kg bw/day:** ↑ ALAT in liver, ↑ relative adrenal weight. **Developmental effects** **780 mg/kg bw/day:** ↑ incidence of palatoschisis (above historical control) at high dose (11 fetuses in 9 litters) vs. control (6 fetuses in 8 litters), low (8 fetuses in 8 litters) and mid-dose (4 fetuses in 6 litters) groups. Two fetuses with exencephaly (vs. one in control and low dose group). ↑ incidence of bipartite sternebrae, non-ossification of forelimb distal phalanx and supernumerary ribs were also noted.

Developmental toxicity Rat–dermal	Wistar, 25/dose **Dermal application** of 0 and 1000 mg/kg bw/day in 1% Cremophor; 6 hour/day GD 6–15	Maternal systemic effects NOAEL = 1000 mg/kg bw/day Maternal dermal effects NOAEL < 1000 mg/kg bw/day LOAEL = 1000 mg/kg bw/day Developmental effects NOAEL = 1000 mg/kg bw/day	**Maternal systemic effects** **1000 mg/kg bw/day:** No signs of systemic toxicity, slight to severe edema and skin scaling noted on GD 7–15 up to one week after treatment period. Slight erythema and scaling noted in control animals on days 9–13. **Developmental effects** No adverse effects observed. Not considered a teratogen in rats.

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES	RESULTS
GENOTOXICITY		
**Gene mutations in bacteria in vitro	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 0–2000 µg/plate	Negative
**Gene mutations in bacteria in vitro	*E. Coli* 0, 625, 1250, 2500, 5000 or 10000 µg/plate	Negative
Gene mutations in bacteria in vitro	*Bacillus subtilis* strains H17 and M45 0.313, 0.625, 1.25, 2.5, 5, 10 and 20 µg/disc with and without activation	Negative
Gene mutations in bacteria in vitro	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 15.6, 31.3, 62.5, 125, 250 or 500 µg/plate with and without activation *E. Coli* wettable powder2uvrA 156, 313, 625, 1250, 2500 or 5000 µg/plate with activation 31.3, 62.5, 125, 250, 500 or 1 000 500 µg/plate without activation	Negative
**Unscheduled DNA synthesis in vitro	Primary rat hepatocytes 0.5–25.2 µl	Negative
**Chromosome aberrations Cytogenic in vitro	Human lymphocytes 0, 3, 10 or 30 µg/mL without activation 0, 30, 100 or 300 µg/mL with activation	Negative
**Chromosome aberrations Sister chromatid exchange in vitro	Chinese hamster ovary cells 4, 8, 15 or 30 µg/mL without activation 15, 30, 60 or 120 µg/mL with activation	Negative

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES		RESULTS
**Chromosome aberrations CHO/HGPRT forward mutation in vitro	Chinese hamster ovary cells 80, 90, 92.5, 95.0, 97.5 or 100 µg/mL without activation 12.5, 25, 50, 100, 150 or 200 µg/mL with activation		Negative
**Micronucleus assay in vivo	NMRI mice 0, 200, 500 or 2000 mg/kg bw		Negative
Dominant lethal assay	Male NMRI SPF–HAN mice Single oral dose of 2000 mg/kg bw (in 1% Cremophor); mating over 4 weeks following dosing, ♀ sacrificed GD 14.		Negative No significant differences in pre/post implantation loss.
SPECIAL STUDIES			
28-day inhalation *Supplemental study for cataract development Cat	Spf Forest of the Dean (4/sex/dose, 6 h per day/ 5 days per week) 0, 0.02, 0.061, 0.309 mg/L/day	NOAEL = 0.309 mg/L/day No LOAEL was determined.	**0.02 mg/L/day**: Cataract in 1 ♂, concluded not to be treatment related due to etiology (developed from a lens vacuole).

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES		RESULTS
Acute neurotoxicity Rat	Fischer 344, 12/sex/dose **Main Study** ♂: 0, 100, 500 or 1000 mg/kg bw/day, single oral dose* ♀: 0, 100, 250 or 500 mg/kg bw/day, single oral dose* *in 0.5% methylcellulose/ 0.4% deionized water at 10 mL/kg **Supplemental Study** 0, 20 or 50 mg/kg, single oral dose* *0.5% methylcellulose/ 0.4% deionized water at 10 mL/kg	NOAEL = 100 mg/kg bw LOAEL = 250/500 (♀/♂) mg/kg bw	**≥ 250 mg/kg bw** (♀): uncoordinated gait, red nasal stain, oral stain, ↓ motor/locomotor activity on day 0 (recovered on day 7), diminished approach, touch and auditory responses, slightly impaired aerial righting, slightly lower body temperature. **≥ 500 mg/kg bw** (♂): uncoordinated gait, ↓ activity, salivation, cool-touch body, lacrimation, staining (urine, red nasal, red lacrimal, oral), ↓ motor/locomotor activity on day 0 (recovered on day 7), diminished approach, touch, auditory and tail pinch responses, impaired aerial righting, lower body temp. **1000 mg/kg bw**: 6/12 ♂ died day 1–2 Signs appeared day 0, until 3–5 days post treatment. **Supplemental study** No treatment related effects observed.
Subchronic neurotoxicity Rat	Fischer, 12/sex/dose 0, 100, 400 or 1600 ppm in the diet ♂: 0, 7.57, 29.2 or 107 mg/kg bw/day ♀: 0, 8.81, 34.0 or 122 mg/kg bw/day	**Systemic toxicity:** NOAEL = 400 ppm (♂ = 29.2 mg/kg bw/day; ♀ = 34 mg/kg bw/day) LOAEL = 1600 pm (♂ = 107 mg/kg bw/day, ♀ = 122 mg/kg bw/day) **Neurotoxicity:** NOAEL = 1600 ppm (♂ = 107 mg/kg bw/day, ♀ = 122 mg/kg bw/day) LOAEL was not determined.	**Systemic Toxicity** **1600 ppm:** ↓bwg (16% ♂, 20% ♀), ↓terminal bw (♂), ↑ rel. brain weight (10%) (♂) **Neurotoxicity:** No treatment related effects observed.

STUDY	SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES		RESULTS
Developmental neurotoxicity Rat	Sprague Dawley, 25 dams/dose 0, 100, 300 or 1000 ppm in the diet (0, 8.8, 22 or 65 mg/kg bw/day)	**Systemic toxicity:** NOAEL = 300 ppm (22 mg/kg bw/day) LOAEL = 1000 pm (65 mg/kg bw/day) **Developmental toxicity:** NOAEL = 300 ppm (22 mg/kg bw/day) LOAEL = 1000 ppm (65 mg/kg bw/day) **Neurotoxicity:** NOAEL = 1000 ppm (65 mg/kg bw/day)	**Systemic toxicity** **1000 ppm:** ↓ maternal bw and bwg during gestation and lactation, ↓ food consumption during gestation and up to day 12 of lactation. **Developmental toxicity** **1000 ppm:** ↓ no. of litters, ↓ gestation index, ↑ duration of gestation, ↑ no. of stillborn pups, ↓ viability index, ↓ preweaning pup bw., delay in eye opening. ↓ brain weight. **Neurotoxicity:** No treatment related effects were observed.
Compound-induced mortality: Rat 28 day dietary—One death (♀) at 300 mg/kg bw/day (also one death in control). Rat 90 day dietary—Two deaths (1 ♂, 1 ♀) at 171.7/235.2 mg/kg bw (♂/♀). Dog 90 day dietary—One death (♂) at 214.8 mg/kg bw/day. Rat multigeneration reproduction—One death (♀) at 103.1 mg/kg bw/day. Acute neurotoxicity: 6/12 ♂ died on days 1–2 at 1000 mg/kg bw			

Appendix II Occupational Exposure Summary

Table 1 Exposure Estimates and MOEs for OPEN Mix, Load and Application of Folicur 432F Foliar Fungicide to Wheat

	Farmers Mix, Load, Application 100 ha/day	**Custom Applicators** Mix, Load, Application 300 ha/day	**Aerial Applicators** Mix, Load, Application 490 ha/day	
Exposure and MOE	**Open Cab**	**Closed Cab**	**Mix/Load**	**Application**
Single layer (long-sleeved shirt and long pants; gloves during mix/load, no gloves during application)				
PHED unit exposure (μg/kg a.i.)[a]	23.59	17.21	14.39	2.49
MOE[c]	706	323	236	1369
Cotton coveralls over single layer (gloves during mix/load, no gloves during application)				
PHED unit exposure (μg/kg a.i.)	16.0125	10.9575	9.7925	1.8425
Daily dose (mg/kg bw/day)	0.0029	0.0059	0.0086	0.0016
MOE	1041	507	347	1846
Daily dose (mg/kg bw/day)[b]	0.0042	0.0093	0.0127	0.0022

[a] Based on a dermal absorption of 25%.

[b] Daily dose calculate as (application rate [kg a.i./ha] × area treated/day [ha/day] × PHED unit exposure [μg a.i./kg a.i.]) / (1000 [μg/mg] × bw [kg]).

[c] MOE based on NOAEL of 3.0 mg/kg bw/day from the mouse developmental toxicity study. The target MOE is 1000.

Table 2 PHED Exposure Estimates and MOEs for CLOSED Mix, Load and Application of Folicur 432F Foliar Fungicide to Wheat

	Custom Applicators (MLA) Mix, Load, Application 300 ha/day	**Aerial Applicators** Mix, Load, Application 490 ha/day	
Exposure and MOE	**Closed Cab**	**Mix/Load**	**Application**
Single layer (long-sleeved shirt and long pants; gloves during mix/load, no gloves during application)			
PHED unit exposure (µg/kg a.i.)[a]	7.67	4.85	2.49
Daily dose (mg/kg bw/day)[b]	0.0041	0.0043	0.0022
MOE[c]	724	702	1369
Cotton coveralls over single layer (gloves during mix/load, no gloves during application)			
PHED unit exposure (µg/kg a.i.)	3.68	2.51	1.84
Daily dose (mg/kg bw/day)	0.002	0.0022	0.0016
MOE	1511	1354	1846

[a] Based on a dermal absorption of 25%.

[b] Daily dose calculate as (application rate [kg a.i./ha] × area treated/day [ha/day] × PHED Unit Exposure [µg a.i./kg a.i.]) / (1000 [µg/mg] × bw [kg]).

[c] MOE based on NOAEL of 3.0 mg/kg bw/day from the mouse developmental toxicity study. The target MOE is 1000.

Table 3 PHED Exposure Estimates and MOEs for Mix/Load Apply of Folicur 432F Foliar Fungicide to Wheat

	Farmers (MLA) Mix, Load, Apply 100 ha/day	**Custom Applicators (MLA)** Mix, Load, Apply 300 ha/day	**Aerial Applicators** Mix, Load, Apply 490 ha/day	
Exposure and MOE	**Open Cab**	**Closed Cab**	**Mix/Load**	**Apply**
Open mix load (gloves coveralls) and apply (open cab—coveralls gloves; closed cab-single layer no gloves; aerial-single layer no gloves)				
PHED unit exposure (µg/kg a.i.)[a]	16.01	12.62	9.79	2.49
Daily dose (mg/kg bw/day)[b]	0.0029	0.0068	0.0086	0.0022
MOE[c]	1041	440	347	1369
Closed mix/load (gloves coveralls) and apply (open cab—coveralls gloves; closed cab-single layer no gloves; aerial-single layer no gloves)				
PHED unit exposure (µg/kg a.i.)	Not applicable	5.34	2.51	2.49
Daily dose (mg/kg bw/day)	Not applicable	0.0029	0.0022	0.0022
MOE	Not applicable	1041	1354	1369

[a] Based on a dermal absorption of 25%.

[b] Daily dose calculate as (application rate [kg a.i./ha] × area treated/day [ha/day] × PHED Unit Exposure [µg a.i./kg a.i.]) / (1000 [µg/mg] × bw [kg]).

[c] MOE based on NOAEL of 3.0 mg/kg bw/day from the mouse developmental toxicity study. The target MOE is 1000.

Table 4 LADD and Cancer Risk Estimates for Farmers and Custom/Aerial Applicators Handling Folicur 432F Foliar Fungicide During Open Mix/Load and Application Activities

Exposure Scenario	Number of Days Exposed/Season	Daily Dose[a] mg/kg bw/day	LADD[b] mg/kg bw/day)	Cancer Risk [c] (unitless)
Farmers: open mix/load + apply (open cab)	2	0.0024	6.89×10^{-6}	4.961×10^{-8}
Custom applicators: closed mix/load + apply (Closed cab)	30	0.002	8.71×10^{-5}	7.44×10^{-7}
Aerial application: closed mix/load	15	0.0022	4.86×10^{-5}	2.86×10^{-7}
Aerial application: apply (aerial–closed cab)	15	0.0016	3.56×10^{-5}	2.83×10^{-7}

[a] Based on the PHED dermal exposure (adjusted for 25% dermal absorption) and inhalation exposure.

[b] Based on application rate of 0.126 kg a.i./ha, exposure frequency of 2 days/year for farmers, 30 days/year for custom applicators and 15 days/year for aerial applicators; a 40-year working tenure and a 75-year life expectancy.

[c] Cancer risk calculated as $Q^{1*} \times$ LADD, where $Q^{1*} = 0.00589$ (mg/kg bw/day)$^{-1}$

* Based on exposure values from Appendix II, Table 3

Table 5 Re-Entry Exposure Estimates and MOEs for Agricultural Workers Re-Entering Wheat Fields Treated with Folicur 432F Foliar Fungicide

Days After Last Application	DFR µg/cm²	Daily Dose[a] mg/kg bw/day	MOE[b]
Day 0	0.252	0.0054	556
Day 2	0.204	0.0044	682
Day 6	0.134	0.0029	1034

[a] Based on a dermal absorption of 25%, 4 hours exposure/day and a 70 kg body weight. Daily dose calculate as (DFR [µg/cm²] × transfer coefficient [cm²/hr] × dermal absorption × 4 [hr/day]) / (bw [kg] × 1000 [µg/mg]).

[b] MOE based on NOAEL of 3.0 mg/kg bw/day from the mouse developmental toxicity study. The target MOE is 1000.

Table 6 LADD and Cancer Risk Estimates During Re-Entry Activities (i.e., scouting)*

Exposure Scenario	Max. No. of Days Exposed/Season	Daily Dose[a] mg/kg-bw/day	LADD[b] mg/kg bw/day	Cancer Risk[c] (unitless)
Postapplication activities: scouting				
Farmers	12	0.0029	5.03×10^{-5}	2.96×10^{-7}
Professional scout	30	0.0029	1.26×10^{-4}	7.41×10^{-7}
Total cancer risk for farmers (14 days/season: 2 mix/load/apply open cab plus 12 days re-entry)				
Farmers mix/load/apply + re-entry	14	0.0052	1.07×10^{-4}	6.30×10^{-7}

[a] Based on the PHED dermal exposure (adjusted for 25% dermal absorption) plus inhalation exposure.

[b] Based on application rate of 0.126 kg a.i./ha, exposure frequency of 2 days/year for farmers, 30 days/year for custom applicators and 15 day/year for aerial applicators; a 40-year working tenure and a 75-year life expectancy.

[c] Cancer risk calculated as $Q^{1*} \times$ LADD, where $Q^{1*} = 0.00589$ (mg/kg bw/day)$^{-1}$

* Based on exposure values from Appendix II, Table 5

Table 7 Number and Location of Additional Crop Field Trials

Zone	**5**	**7**	**7A**	**14**	**Total**
Guideline requirements	**2**	**7**	**1**	**10**	**20**
Submitted by registrant	**3**	**4**	**0**	**3**	**10**
Additional field trials	**0**	**3**	**1**	**7**	**11**

Table 8 Number and Location of Additional Crop Field Trials (25% reduction)

Zone	5	7	7A	14	Total
Guideline requirements	2	5	1	7	15
Submitted by registrant	3	4	0	3	10
Additional field trials	0	1	1	4	6

Appendix III Residues

Table 1 Integrated Food Residue Chemistry Summary

Direction for Use

Crop	Formulation Type	Rate (g a.i./ha)	Application/ Season	Maximum Rate g a.i./ha	PHI (days)
Wheat	Suspension	126	1	126	30

Physicochemical Properties

Water solubility (mg/L)	21 at 10°C 32 at 20°C 52 at 40°C
Solvent solubility at 25°C (g/L)	Hexane 0.08 Toluene 57 2-propanol 99 Acetone > 200 CH_2Cl_2 > 200 Dichloromethane > 200
n-octanol/water partition coefficient (log K_{ow}) at 20°C	3.7
Dissociation constant (pKa)	Not applicable (no dissociable functionality)
Vapour pressure (Pa)	1.3×10^{-6} Pa
Relative density (g/mL)	1.202 (temperature not reported)
Melting point	104.7°C
UV–Visible absorption spectrum	Maximum at 220.8 nm in acetonitrile-buffer, at pH 4, 7 and 9. No absorbance at $\lambda > 300$ nm

Analytical Methodology

Parameters	**Plant Matrices**		
Method ID	101341	108114	94295
Type	**Enforcement**, data-gathering	Data-gathering	Data-gathering
Analyte	Tebuconazole	Tebuconazole	Tebuconazole
Instrumentation	GC/NPD	LC-MS/MS	GC/NPD

Method ID	101341	108114	94295
LOQ	**Wheat** ppm Grain 0.05 Straw 0.1 Forage 0.1 Hay 0.1	**Wheat** ppm Grain 0.01 Straw 0.05 or 0.01 Forage 0.01 Hay 0.05 or 0.1 Flour 0.01 Bran 0.01 Shorts 0.01 Germ 0.01 Middlings 0.01 Aspirated grain fractions 0.01	**Wheat** ppm Grain 0.01 Straw 0.01 or 0.06 Forage 0.02 Flour 0.01 Bran 0.01 Shorts 0.02 Middlings 0.01 **Turnip** Tops 0.02 Roots 0.03 **Spinach** Leaves 0.02
Standard	External: tebuconazole	Internal: [$^{15}N_3$] tebuconazole	External: tebuconazole
ILV	Successfully performed on peanut shells, soapstock, hay, nutmeat and oil	Not submitted	Not submitted
Extraction	Acetone:water (3:1, v:v)	Acetone:water (3:1, v:v)	Acetone:water (3:1, v:v)
Clean-up	Gel permeation, silica gel and C18 chromatography	Particulate filtration followed by tandem mass-spectrometry	Gel permeation and silica gel chromatography
Multiresidue method	Tebuconazole was tested through Protocols A to F according to the procedures described in PAM Vol. I, USFDA. The findings indicated that recovery of tebuconazole was too low, resulting in unacceptable accuracy or interference, precluding determination of the analyte. Thus, multiresidue methods as described in the USFDA, PAM Vol. I are not suitable for determination of tebuconazole.		

<table>
<tr><th colspan="4">Analytical Methodology</th></tr>
<tr><th>Parameters</th><th colspan="3">Animal Matrices</th></tr>
<tr><td>Method ID</td><td colspan="3">101316</td></tr>
<tr><td>Type</td><td colspan="3">Enforcement, data-gathering</td></tr>
<tr><td>Analytes</td><td colspan="3">Tebuconazole and hydroxy tebuconazole</td></tr>
<tr><td>Instrumentation</td><td colspan="3">GC/NPD, MS-SIM</td></tr>
<tr><td rowspan="3">LOQ</td><td></td><td>(HWG 1608)
Tebuconazole</td><td>(HWG 2061)
Hydroxy Tebuconazole</td></tr>
<tr><td>Bovine liver, kidney, muscle; and poultry liver, muscle, fat, skin, eggs</td><td>0.1 ppm</td><td>0.1 ppm</td></tr>
<tr><td>Bovine milk</td><td>0.05 ppm</td><td>0.05 ppm</td></tr>
<tr><td>Standard</td><td colspan="3">External: tebuconazole and hydroxy tebuconazole</td></tr>
</table>

ILV	Successfully performed on milk, egg, bovine liver, kidney, muscle and fat; and poultry liver, muscle, fat and skin
Extraction/clean-up	Extraction: methanol or hexane/methanol; partitioned in Clean-up: gel permeation and C18 chromatography
Multiresidue method	Tebuconazole and the metabolite hydroxy tebuconazole, were subjected to testing by the procedures described in Protocols A to F of PAM Vol. I, USFDA. Results indicated that either the analyte did not produce chromatographic response or problems were encountered with interferences, very low recoveries and very poor precision between duplicate analyses. Thus, multiresidue methods as described in the USFDA, PAM Vol. I are not suitable for determination of tebuconazole and the metabolite hydroxy tebuconazole.

Nature of the Residue in Wheat

Radiolabel	[Triazole-UL-^{14}C] tebuconazole	[Triazole-^{14}C] tebuconazole
Test site	Greenhouse microplots containing sandy loam soil	Greenhouse microplots containing sandy loam soil
Treatment	A single **foliar** spray at the boot stage of growth	**Seed** treatment
Rate	500 g a.i./ha	11 g a.i./100 kg seed
End-use product	Folicur 22.5% Dry Flowable (DF)	Not provided
PHI	50 days	38 (forage) and 66 days (mature wheat) postplanting

Foliar treatment
Tebuconazole is the major metabolite (56 to 99% TRRs) observed in wheat foliage indicating little or no metabolism of tebuconazole occurring in the foliage of the plant. In contrast, wheat grain contains small amount of tebuconazole (6% TRRs) indicating extensive metabolism of the parent occurs. The major metabolic products in the grain are triazolylalanine (80% TRRs) and triazolylacetic acid (13% TRRs) demonstrating that cleavage of the parent molecule occurs resulting in the liberation of the triazole ring with further modification to form triazolylalanine and triazolylacetic acid.

Seed treatment
Low levels of radioactivity were translocated from seed to forage, grain and chaff. Consequently, characterization of the metabolites was not performed in these matrices. Major metabolites observed in wheat straw are tebuconazole (25% TRRs), its hydroxylated product (HWG 2061; ~15% TRRs) and glucoside conjugate of this hydroxylated product (~15% TRRs). Tebuconazole is also a major metabolite in the root part (76% TRRs).

Metabolites identified	**Major metabolites (> 10% TRRs)**		**Minor metabolites (< 10% TRRs)**	
Radiolabel	**[Triazole-UL-^{14}C] tebuconazole (foliar treatment)**	**[Triazole-^{14}C] tebuconazole (seed treatment)**	**[Triazole-UL-^{14}C] tebuconazole (foliar treatment)**	**[Triazole-^{14}C] tebuconazole (seed treatment)**
Wheat grain	Triazolylalanine, triazolylacetic acid	Metabolites not characterized due to low concentrations	Tebuconazole, hydroxy tebuconazole (< 1% TRRs)	Metabolites not characterized due to low concentrations

Wheat straw	Tebuconazole	Tebuconazole, hydroxy tebuconazole, hydroxy tebuconazole glucoside	Unidentified bound residues	Not characterized due to low concentrations
Wheat chaff	Tebuconazole	Not characterized due to low concentrations	Triazolyalanine	Not characterized due to low concentrations
Wheat forage	Tebuconazole	Not characterized due to low concentrations	Unidentified bound residues	Not characterized due to low concentrations
Wheat roots	Not analyzed	Tebuconazole	Not analyzed	Not characterized due to low concentrations

Supplemental information: GRAPE and PEANUT metabolism studies

Grape

Tebuconazole, radiolabelled in the phenyl-ring, was applied as a foliar spray, to Niagara White vines and grapes at a rate of 280 g a.i./ha. The plants were grown in microplots in a plastic shelter. Grape samples were taken at 0, 3, 7, 14, 21, and 28 days post treatment.

Total ^{14}C residues declined throughout the sampling period from 6.9 ppm at day 0 to 2.3 ppm at day 28. The extractable residues from grapes accounted for 93.1–97.6% of TRRs. At all time intervals, the majority of the recovered radioactivity ($\geq$ 85% of TRRs) was found on the surface (ethanol/dichloromethane rinse) of the fruit. Following the ethanol/dichloromethane rinse, grapes were macerated and extracted with methanol. Residues in the methanol extract were $\leq$ 6.1% of TRRs. Residues in the marc ranged between 0.1% of TRRs at 0 day and 6.3% of TRRs at 28 days. Methanol reflux of the extracted macerate recovered a further 4.9% of the 6.3% bound TRRs for the 21 and 28 day samples. Approximately 89% of the radioactivity in the water-soluble fraction was released by cellulase hydrolysis while no release of radioactivity was observed with ß-glucosidase hydrolysis.

The majority of the TRRs (84.5–99.1%) were found in the surface rinse and were identified as the parent compound, tebuconazole. The residues in the methanol reflux (7.8–10.7% TRRs) were identified as parent compound, as well. About 95% of the TRRs at various intervals post treatment were identified as parent compound.

Peanut

Three metabolism studies were conducted on peanuts.

Study no. 1

Tebuconazole, radiolabelled in the phenyl-ring, was applied as 3 foliar sprays at the rate of 250 g a.i./ha to peanut plants, growing in sandy loam soil in a greenhouse, at 6, 8 and 10 weeks after planting for a total rate of 750 g a.i./ha. Foliage, shells and kernels were harvested 98 days after the last application.

TRR levels in foliage, shells and kernels were 22.60 ppm, 0.27 ppm and 0.09 ppm respectively. Approximately 94.5% of the TRRs in foliage were extracted using methanol and aqueous methanol and 5.5% remained unextractable. The parent compound tebuconazole made up 59.6% of the TRRs and the metabolite HWG 2061 contributed to 13.2% of the TRRs in foliage.

Similarly, in shells, 57.3% of TRRs was extracted with methanol and aqueous methanol while 14.4% was released via acid (HCl) hydrolysis. In shells, 28.2% of the TRRs was unextractable. The parent compound tebuconazole contributed to 15.9% of the TRRs while HWG 2061 contributed to 3.9% of the TRRs.

Total residues in peanut kernels were very low (0.09 ppm), and 46% of the TRRs were associated with the oil fraction extracted with hexane. Acid hydrolysis of the meal remaining after hexane extraction resulted in release of 50.6% of the TRRs. Approximately 3.4% of the TRRs was not extractable. The radioactivity in the kernels could not be identified.

Study no. 2
Tebuconazole radiolabelled in the phenyl-ring was applied as 7 foliar sprays to peanut plants at a rate of 204 g a.i./ha 6, 9, 11, 13, 15, 17 and 19 weeks after planting for a total rate of 1.4 kg a.i./ha. Peanut kernels, foliage and shells were collected at a 10-day PHI for analysis. Samples were allowed to air dry for 4 days prior to processing to simulate normal agricultural practices. Total radioactive residues were 110 ± 13 ppm in forage, 17.7 ± 1.38 ppm in shells and 0.545 ± 0.024 ppm in kernels.

Peanut kernels were subjected to a series of sequential extractions in an attempt to characterize and identify the radioactivity. Approximately 39% of the TRRs were extractable into acetone water (0.212 ppm) and 30% of the TRRs (0.164 ppm) were extractable into hexane. Four percent (0.022 ppm) of TRRs were extractable into chloroform/ methanol while 23% of the TRRs was released via acid hydrolysis. Approximately 19% of TRRs were identified as tebuconazole, 30% was associated with fatty acids and 4% was associated with bound lipids. The remaining extractable residues were not identified.

In peanut forage, 88% was extracted with methanol and water, 5% of the TRRs which remained in the solid fraction was released by acid hydrolysis and 6% remained non extractable. Tebuconazole accounted for 69.6% of the TRRs (77.2 ppm) and the metabolites HWG 2061 and HWG 2606 accounted for 7.4% (6.7 ppm) and 1.2% (1.3 ppm) of TRRs, respectively.

In peanut shells 54% of TRRs were extractable with methanol/water. The remaining solids were subjected to 1N and 6N HCl hydrolysis, which released 19% and 5% of the TRRs, respectively. Approximately 22% of the TRRs remained non extractable. Tebuconazole contributed to 57.8% of the TRRs and the metabolites HWG 2061 and HWG 2606 accounted for 4.4% and 1.1% of the TRRs, respectively.

Study no. 3
Peanut plants were treated with 3 foliar applications of triazole labelled tebuconazole at a rate of 250 g a.i./ha for a total rate of 750 g a.i./ha. The mature crop was harvested at a 49 day PHI. TTR levels were 29.2 ppm in foliage, 1.19 ppm in nuts and 0.16 ppm in shells.

In nuts, approximately 92.3% of the TRRs were extractable with hexane followed by methanol/water and 7.1% of TRRs were released via acid hydrolysis. Unextractable residues made up 0.6% of the TRRs. Triazolylalanine, triazole and triazolyllactic acid, the only components that were identified, made up 46.4%, 9.0% and 8.5% of the TRRs respectively.

In foliage, 93.6% of TRRs were extractable with methanol, aqueous methanol and aqueous methanol reflux and 6.4% remained non-extractable. Identified components were tebuconazole (58.4% of TRRs) and HWG 2061 (15.1% of TRRs).

In shells, 71.5% of the TRRs were extractable with aqueous methanol and aqueous methanol reflux. Acid hydrolysis of the unextracted portion released 8.6% of the TRRs. Approximately 19.9% of the TRRs remained non-extractable. The parent compound tebuconazole accounted for 15.6% of the TRRs. Also identified were the metabolite HWG 2061 (3.4% of TRRs) and triazolylalanine (2.6% of TRRs).

Overall summary
The major terminal residue for foliar treated wheat, grape and peanuts was the parent compound tebuconazole in all commodities except peanut kernels and wheat grain. The major residues in these two commodities were triazolylalanine, triazolylacetic acid and triazolyllactic acid (peanut only) and triazole (peanut only).

Due to the lack of information on wheat metabolism study using phenyl ring label, residue of concern in 3 diverse crops cannot be defined. Since the current submission is on wheat only, based on wheat metabolism study using triazole ring label and additional information from peanut and grape metabolism studies, the residue of concern in wheat can be defined as tebuconazole.

Confined Rotational Crop Study			
Crops	Wheat, kale and red table beet	Wheat, kale and red table beet	Wheat
Radiolabel	[Triazole-3,5-^{14}C] tebuconazole	[Phenyl-UL-^{14}C] tebuconazole	[Phenyl-UL-^{14}C] tebuconazole
Test site	Sandy loam soil	Greenhouse microplot containing sandy loam soil	Greenhouse microplot containing sandy loam soil
Treatment	Radiolabel was applied as a foliar spray to wheat; the wheat was harvested and the soil was retreated with the same dose; rotational crops were planted 29, 122 and 273 days after treatment of soil	Radiolabel was applied once to soil; rotational crops were planted 30, 136 and 273 days after treatment of soil	Radiolabel was applied once to soil; the rotational crop was planted 32, 152, 272* and 363* days after treatment of soil
Rate	1st treatment—500 g a.i./ha (foliar spray) 2nd treatment—500 g a.i./ha (soil treatment)	560 g a.i./ha	2520 g a.i./ha
End-use product	Not provided	22.5% dry flowable	3.6F flowable liquid
PHI (days)	Immature wheat—43 Mature wheat—85 to 99 Kale—58 to 85 Beet roots and tops—58 to 107	Immature wheat—50 to 55 Mature wheat—88 to 105 Kale—34 to 70 Beet roots and tops—88 to 132	Immature wheat—49 to 55 Mature wheat—92 to 111

* Due to crop failure (explanation unclear), crop samples from these post-treatment intervals were not analyzed.

Exaggerated rates (4.4× to 20×) were used in all 3 confined rotational crop studies. The results demonstrated that there was uptake of residues from soil by the rotational crops. TRRs in the rotational crops were all higher than 0.01 ppm at all plantback intervals, this triggers field accumulation in rotational crop study.

Results from the triazole-ring radiolabel study demonstrated that tebuconazole was extensively metabolized in the rotational crops kale, red table beet and wheat into 3 major products: triazolylalanine (31–80% TRRs), triazolylacetic acid (21–54% TRRs) and triazolyllactic acid (37–54% TRRs). The amount of tebuconazole in the rotational crops was small, ranging from 1.7–15% TRRs. Triazolylalanine was the major component in the wheat grain, averaging 60.9% TRRs; in beet roots, 55.0% TRRs; and in kale, 73.4% TRRs. Triazolyllactic acid was the major metabolite present in wheat straw, with about 35.7% TRRs; and in beet tops 34.6% TRRs. Triazolylacetic acid accounted for 50.8% TRRs of the radioactivity in the immature wheat.

The metabolic pathway of tebuconazole in the rotational crops involved the cleavage of tebuconazole molecule at the linkage of the triazole ring, giving rise to 3 major metabolites: triazolylalanine, triazolyllactic acid and triazolylacetic acid.

Findings from one phenyl-ring radiolabel study indicated that tebuconazole was the predominant residues in kale, beet tops and beet roots harvested from crops planted at all treatment intervals. These matrices also contained a significant amount of radioactivity that was aqueous in nature.

In wheat, TRRs were highest in straw, followed by immature wheat/chaff and grain. Tebuconazole was the predominant residues in immature wheat, wheat straw and chaff. The highest proportion of tebuconazole (35% to 45% TRRs) occurred in immature wheat. In contrast, wheat grain contained very low amount of radioactivity (non-detectable to 4% TRRs) of organosoluble nature (including tebuconazole). The majority of the radioactivity (55% to 65% TRRs) in the wheat grain resided in the aqueous fraction. This residue profile was consistent with that observed in the second phenyl-ring radiolabel study. Both studies suggested that extensive metabolism of tebuconazole occurred in wheat grain. The nature of the radioactivity in the aqueous fraction of wheat grain was investigated in the second phenyl-ring radiolabel study, and results indicated that the majority of these radioactivity was attributable to 6 anionic polar metabolites.

Sufficient information was generated from the second phenyl-ring radiolabel study to indicate that the metabolic pathway of tebuconazole in the rotational crop wheat proceed via hydroxylation of the parent compound with possible further conjugation. During the metabolic process, loss of chlorine, butyl and methyl groups may occur. Further degradation into smaller polar residues via cleavage at the linkage of the phenyl and triazole rings may also take place. This study was considered supplemental as the rotational crops from the 272- and 363-day post-treatment intervals were not analyzed due to crop failure (explanation unclear).

Soil TRR levels were determined in all studies, and characterization of the radioactivity was carried out in two studies. It was shown that the majority of the extracted radioactivity (close to 90%) in the soil was attributable to tebuconazole.

Field accumulation in rotational crops study

In the field accumulation rotational crop study, soil was treated with 7 applications of tebuconazole at the rate of 250 g a.i./ha/application (total rate: 1750 g a.i./ha/season) made at 14-day intervals using ground equipment. At intervals of 30 and 120 days post-treatment, representative leafy vegetable (spinach), cereal grain (wheat or sorghum) and root (turnip) were planted as rotational crops and grown to maturity. Green forage samples were collected at the 45-day postplanting interval for sorghum and wheat. Residues of tebuconazole were determined on each mature crop, as well as in soil samples. Only cereal straw and forage showed a slight increase in tebuconazole residues at the 120-day plantback interval. No tebuconazole residues above the LOQ could be detected in any of the matrices (wheat grain, turnip roots and spinach) sampled at the 120-day plantback interval, except for cereal forage and cereal straw, which contained residues of 0.05 ppm and 0.11 ppm, respectively.

The proposed label has a plantback interval of 120 days.

Nature of the Residue in Lactating Goat

Species	**Radiolabel**	**Dose level**	**Sacrifice**
Capra hircus (Alpine × Nubian)	[Triazole-3,5-^{14}C] tebuconazole	3 mg/kg bw/day (39 ppm in feed)	2 hours after the last dose
Not provided	[Phenyl-UL-^{14}C] tebuconazole	15 mg/kg bw/day	2 hours after the last dose

Results generated from the two goat metabolism studies conducted with different radiolabels of tebuconazole ([triazole-3,5-^{14}C] or [phenyl-UL-^{14}C]) are similar. TRRs are highest in liver and kidney, followed by fat, muscle and milk. The main metabolite identified in the tissues and milk is the hydroxylation product of the parent compound in conjugated form (hydroxy tebuconazole glucuronide; 46–93% TRRs). The proportion of unchanged parent compound in the tissues and milk is considerably low (0–18% TRRs).

Major metabolic pathway of tebuconazole in goat appears to proceed either via oxidation of the parent compound to hydroxy tebuconazole with further conjugation with glucuronic acid to form hydroxy tebuconazole glucuronide (in liver, kidney, fat, muscle and milk) or conjugation of the parent compound with glucuronic acid to tebuconazole glucuronide (in liver and kidney only). Cleavage of tebuconazole to free-form 1,2,4-triazole does not appear to be a major metabolic route because a significant amount of the metabolite was not observed in the tissues although an unidentified metabolite detected in the methanol extract of milk, with very low TRR levels (0.001 ppm), was shown to have polarity similar to 1,2,4-triazole.

Residue of concern is defined as tebuconazole plus the metabolite hydroxy tebuconazole.

Metabolites identified	**Major metabolites (> 10% TRRs)**		**Minor metabolites (< 10% TRRs)**	
Radiolabel	**[Triazole-3,5-^{14}C] tebuconazole**	**[Phenyl-UL-^{14}C] tebuconazole**	**[Triazole-3,5-^{14}C] tebuconazole**	**[Phenyl-UL-^{14}C] tebuconazole**
Liver	TEU, OH-TEU-glucuronide, TEU-glucuronide	TEU, OH-TEU, OH-TEU-glucuronide	4 unidentified metabolites with polarity similar to TEU, TEU-glucuronide or OH-TEU-glucuronide	No minor metabolites
Kidney	OH-TEU-glucuronide, TEU-glucuronide	OH-TEU-glucuronide	TEU, 1 unidentified metabolite with polarity similar to OH-TEU-glucuronide	TEU, OH-TEU
Muscle	OH-TEU-glucuronide	OH-TEU, OH-TEU-glucuronide	TEU, 3 unidentified metabolites with polarity similar to OH-TEU-glucuronide	No minor metabolites
Fat	TEU, OH-TEU-glucuronide	OH-TEU, OH-TEU-glucuronide	4 unidentified metabolites with polarity similar to OH-TEU-glucuronide	TEU
Milk	OH-TEU-glucuronide	TEU, OH-TEU, OH-TEU-glucuronide	TEU, 8 unidentified metabolites (one has polarity similar to 1,2,4-triazole; others have polarity similar to TEU or OH-TEU-glucuronide)	No minor metabolites

TEU = Tebuconazole
TEU-glucuronide = Tebuconazole glucuronide
OH-TEU = Hydroxy tebuconazole (HWG 2061)
OH-TEU-glucuronide = Hydroxy tebuconazole glucuronide

Nature of the Residue in Laying Hen			
Species	**Radiolabel**	**Dose level**	**Sacrifice**
Gallus domesticus	[Triazole-3,5-^{14}C] tebuconazole	2 mg/kg bw/day (30 ppm in feed)	30 minutes after the last dose
Gallus gallus	[Phenyl-UL-^{14}C] tebuconazole	10 mg/kg bw/day	30 minutes after the last dose
Not provided	[Phenyl-UL-^{14}C] tebuconazole	10 mg/kg bw/day	3.5 hours after the last dose

Results from the three-hen metabolism studies conducted with different radiolabels of tebuconazole ([triazole-3,5-^{14}C] or [phenyl-UL-^{14}C]) are similar. TRRs are highest in liver, followed by kidney and other tissues (fat, skin, gizzard and heart); muscle and eggs contain the lowest TRRs. Tebuconazole and hydroxy tebuconazole are present in all matrices with TRRs ranging from 2–94% and 3–49%, respectively. The metabolites, ECW 4390 and HWG 2443, show a restricted tissue distribution and are present in liver, kidney, skin, muscle and eggs, with TRRs ranging from 4–72% and 6–51%, respectively.

The major metabolic pathway involves oxidation of tebuconazole to hydroxy tebuconazole. The oxidation product is further conjugated with either sulfate or glucuronic acid to form ECW 4390 and hydroxy tebuconazole glucuronide, respectively; or it is further oxidized to HWG 2443 with further conjugation with glucuronic acid to form tebuconazole acid glucuronide. A small amount of 1,2,4-triazole (11 to 14% TRRs) is present in muscle and eggs, indicating that cleavage of tebuconazole to this molecule is a minor metabolic pathway in these matrices.

Residue of concern is defined as tebuconazole plus the metabolite hydroxy tebuconazole.

Metabolites identified	**Major metabolites (> 10% TRRs)**		
Radiolabel	**[Triazole-3,5-^{14}C] tebuconazole**	**[Phenyl-UL-^{14}C] tebuconazole**	
	Sacrifice (0.5 hour)	**Sacrifice (0.5 hour)**	**Sacrifice (3.5 hours)**
Egg	TEU, OH-TEU, 1,2,4-triazole	TEU, OH-TEU, TEU-acid	TEU, OH-TEU
Liver	TEU, OH-TEU, OH-TEU-sulfate, TEU-acid	TEU, OH-TEU, OH-TEU-sulfate, TEU-acid	OH-TEU-sulfate, TEU-acid
Kidney	Not analyzed	TEU, OH-TEU-sulfate, TEU-acid	OH-TEU-sulfate, TEU-acid
Muscle: leg and breast	TEU, OH-TEU, 1,2,4-triazole	Not analyzed	Not analyzed
Muscle: breast	Not analyzed	TEU, OH-TEU	TEU, OH-TEU, OH-TEU-sulfate
Muscle: thigh	Not analyzed	Not analyzed	TEU, OH-TEU
Fat	TEU, OH-TEU	TEU, OH-TEU	TEU
Skin	Not analyzed	TEU, OH-TEU	TEU, OH-TEU
Heart	Not analyzed	TEU, OH-TEU	Not analyzed

Gizzard	Not analyzed	TEU	Not analyze

OH-TEU-sulfate = Hydroxy tebuconazole sulfate (ECW 4390)   TEU-acid = Tebuconazole acid (HWG 2443)
TEU-acid-glucuronide = Tebuconazole acid glucuronide

Metabolites identified	**Minor metabolites (< 10% TRRs)**		
Radiolabel	**[Triazole-3,5-^{14}C] tebuconazole Sacrifice (0.5 hour)**	**[Phenyl-UL-^{14}C] tebuconazole**	
		Sacrifice (0.5 hour)	**Sacrifice (3.5 hours)**
Egg	10 unidentified metabolites with polarity similar to TEU, OH-TEU, OH-TEU-glucuronide or TEU-acid-glucuronide	Unidentified metabolite(s)	OH-TEU-sulfate
Liver	TEU-acid-glucuronide, OH-TEU-glucuronide, 2 unidentified metabolites of which 1 has polarity similar to OH-TEU-glucuronide, the other has polarity between TEU and OH-TEU	Unidentified metabolite(s)	TEU, OH-TEU
Kidney	Not analyzed	OH-TEU, Unidentified metabolite(s)	TEU, OH-TEU
Muscle: leg and breast	4 unidentified metabolites with polarity similar to OH-TEU-sulfate or TEU-acid	Not analyzed	Not analyzed
Muscle: breast	Not analyzed	Unidentified metabolite(s)	No minor metabolites
Muscle: thigh	Not analyzed	Not analyzed	OH-TEU-sulfate
Fat	4 unidentified metabolites with polarity similar to OH-TEU-sulfate or TEU-acid	Unidentified metabolite(s)	OH-TEU
Skin	Not analyzed	Unidentified metabolite(s)	TEU-acid
Heart	Not analyzed	Unidentified metabolite(s)	Not analyzed
Gizzard	Not analyzed	OH-TEU, Unidentified metabolite(s)	Not analyzed

Crop Field Trials–Wheat

A total of 73 field trials on wheat were submitted. Out of these 73 field trials, 53 were conducted in Canadian representative zones. Of these 53 trials, only 4 trials (2 in Zone 5; 1 in Zone 7; and 1 in Zone 14) were carried out at GAP. The rest were either carried out at exaggerated rates (2.5× to 3× GAP) or had an unacceptably long PHI (37–97 days).

Commodity	Rate g a.i./ha	PHI (days)	Tebuconazole Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	SD
Wheat grain	123–128	33–39	8	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	N/A
	126[*]	32–37	8	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	N/A
	126[*]	41–69	28	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	N/A
	123–132	62–97	26	< 0.01	0.03	0.02	0.01	0.011	0.004
	147	67	2	< 0.05	< 0.05	N/A	N/A	N/A	N/A
	184–188	33–39	10	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	N/A
	308–385	25–61	62	< 0.01	0.84[**]	0.64	0.01	0.045	0.12

[*] American residue data previously reviewed. It was noted that out of the 19 field trials, 9 (with PHIs of 32 to 69 days) were carried out in applicable Canadian representative zones for wheat.

[**] The residue value, 0.84 ppm, was observed in the field trial that received the highest total treatment rate of 385 g a.i./ha/season (the other grain sample from this trial showed a residue value of 0.44 ppm). These values were confirmed by quadruplicate extraction and analysis of the samples.

Residue Decline

There were residue decline studies carried out on wheat grain, forage, hay and straw. They were all carried out in applicable Canadian representative zones (7 and 14). In addition, there were two decline trials on wheat hay that were carried out in Zone 5 (Canadian representative zone) and Zone 4 (American zone). Exaggerated rates (~2.5× of GAP) were used in all these trials except for trials on wheat forage (3 trials), which were either carried out with rates at one-half (0.5×) or near GAP (0.98× or 1.04×).

Commodity	Zone	Rate (g a.i./ha/season)	PHI (days)	Tebuconazole Residues (ppm) [average]
Wheat grain	7	317	40	0.025, 0.022 [0.024]
			46	0.029, 0.024 [0.027]
			52	0.044, 0.037 [0.041]
			56	0.011, 0.014 [0.013]
	14	311	37	0.070, 0.072 [0.071]
			42	0.198, 0.118 [0.158]
			47	0.069, 0.047 [0.058]
			54	0.067, 0.054 [0.061]

Proposed Maximum Residue Limits

No MRL is being proposed as a result of the review of this submission on the foliar use. There are insufficient residue trials to support the proposal of any MRL. Currently, there is an existing MRL of 0.05 ppm in Canada for tebuconazole residues in/on wheat. The MRL was promulgated in an earlier import submission on the foliar use of tebuconazole and is harmonized with the American tolerance and Codex MRL.

FIELD ACCUMULATION IN ROTATIONAL Crops—Wheat, Sorghum, Spinach and Turnip

Field accumulation in rotational crops study was conducted at 2 sites in the United States (Kansas and Indiana) in Zone 5 (Canadian representative zone). Soil (sandy loam in the Indiana site; silty clay loam in the Kansas site) was treated with 7 applications of Folicur 1.2 EC formulation at the rate of 250 g a.i./ha/application made at 14-day intervals for a total rate of 1750 g a.i./ha. At intervals of 30 and 120 days post-treatment, representative leafy vegetable (spinach), cereal grain (wheat or sorghum) and root (turnip) rotational crops were planted and grown to maturity. Tebuconazole residues in the mature crops were measured.

Commodity	Plantback interval (days)	Tebuconazole residues (ppm)	
		Maximum levels	LOQ of analytical method
Cereal grain	30	0.03	0.01
	120	0.01 (at LOQ)	
Cereal straw	30	0.04 (< LOQ)	0.06
	120	0.11	
Cereal forage	30	0.01 (< LOQ)	0.02
	120	0.05	
Spinach leaves	30	0.02	0.02
	120	0.02 (at LOQ)	
Turnip tops	30	0.03	0.02
	120	< 0.02 (< LOQ)	
Turnip toots	30	0.03	0.03
	120	< 0.03 (< LOQ)	

Processing Study

Three processing studies were conducted on wheat. In two of the studies, tebuconazole residues in the wheat grain RAC were less than the LOQ, despite the exaggerated rate used; hence, concentration factors could not be reliably obtained. In the third study, quantifiable residues of tebuconazole were observed in the wheat grain RAC, and concentration factors for the processed fractions of flour, bran, shorts and middlings were reported. The results showed no concentration of tebuconazole residues in the processed fractions of wheat flour and bran.

Study No.	**107526 (5× GAP)**		**220287 (12× GAP)**		**98032* (4× GAP)**	
Wheat matrix	Mean residue levels (ppm)	Concen. factor	Mean residue levels (ppm)	Concen. factor	Mean residue levels (ppm)	Concen. factor
Grain RAC	< 0.05 (<LOQ)	N/A	< LOQ**	N/A	0.08	N/A

Study No.	**107526 (5× GAP)**		**220287 (12× GAP)**		**98032* (4× GAP)**	
Wheat matrix	Mean residue levels (ppm)	Concen. factor	Mean residue levels (ppm)	Concen. factor	Mean residue levels (ppm)	Concen. factor
Flour	Not analyzed due to no measurable residues in RAC	Not calculated (sample not analyzed)	< LOQ**	Not calculated due to no measurable residues in RAC	0.01 (patented flour)	0.13
					0.02 (low grade flour)	0.25
Bran	Same	Same	< LOQ**	Same	0.08	1
Shorts	Same	Same	0.012	Same	0.2	2.5
Middlings	Same	Same	< LOQ**	Same	0.05	0.6
Germ	Same	Same	0.02	Same	Not analyzed	Not calculated
Aspirated grain fraction	Same	Same	0.38	Same	Not processed into this commodity	Not calculated

* The end-use product used in this study was Folicur 1.2 EC, whereas Folicur 3.6 F was used in the other two studies. Also, this study was conducted with a PHI of 17 days, while the other 2 studies had PHI of 55 days (Study No. 220287) and 64 days (Study No. 107526).

** Less than LOQ of 0.01 ppm.

Livestock Feeding

Livestock feeding studies were performed on dairy cattle and poultry. In the dairy cattle feeding study, tebuconazole was administered by bolus capsule to 10 Holstein dairy cows (3 cows/group) for a period of 28 days. The dosages were equivalent to 30, 90, and 300 ppm in feed. Milk samples were collected during the dosing period. At the end of the test period, the animals were sacrificed, and the tissues (liver, kidney, muscle and fat) and milk were analyzed for total residues of tebuconazole and the metabolite HWG 2061. In the poultry study, groups of laying hens (12 hens/group) were fed daily rations of feed fortified with tebuconazole at 2, 6 and 20 ppm for 28 days. Upon sacrifice, tissues and eggs from each group were analyzed for tebuconazole and the metabolite HWG 2061.

Residues of Tebuconazole and Hydroxy Tebuconazole (HWG 2061) in Tissues, Milk and Eggs from Lactating Dairy Cattle and Poultry after 28 Days Feeding

CATTLE

		Residues (ppm)		
Cattle		Feeding level (3 animals per dose group)		
Matrix	Analyte	30 ppm	90 ppm	300 ppm
Milk	Tebuconazole	< 0.05, <0.05, < 0.05	< 0.05, < 0.05, < 0.05	< 0.05, < 0.05, < 0.05
	Hydroxy tebuconazole HWG2061	< 0.05, < 0.05, < 0.05	< 0.05, < 0.05, < 0.05	0.06, 0.10, 0.12

	Combined residues*	< 0.1, < 0.1, < 0.1	< 0.1, < 0.1, < 0.1	< 0.11, < 0.15, < 0.17
Fat	Tebuconazole	N/A	N/A	< 0.1, < 0.1, < 0.1
	Hydroxy tebuconazole HWG2061	N/A	N/A	< 0.1, < 0.1, < 0.1
	Combined residues*	N/A	N/A	< 0.2, < 0.2, < 0.2
Muscle	Tebuconazole	N/A	N/A	< 0.1, < 0.1, < 0.1
	Hydroxy tebuconazole HWG2061	N/A	N/A	< 0.1, < 0.1, < 0.1
	Combined residues*	N/A	N/A	< 0.2, < 0.2, < 0.2
Liver	Tebuconazole	< 0.1, < 0.1, < 0.1	0.2, 0.1, 0.2	0.4, 0.8, 0.7
	Hydroxy tebuconazole HWG2061	0.1, < 0.1, < 0.1	0.6, 0.4, 0.6	1.9, 1.5, 1.3
	Combined residues*	< 0.2, < 0.2, < 0.2	0.8, 0.5, 0.8	2.3, 2.3, 2.0
Kidney	Tebuconazole	< 0.1, < 0.1, < 0.1	< 0.1, < 0.1, < 0.1	< 0.1, < 0.1, < 0.1
	Hydroxy tebuconazole HWG2061	< 0.1, < 0.1, < 0.1	0.7, 0.9, 0.6	1.2, 2.2, 1.5
	Combined residues*	< 0.2, < 0.2, < 0.2	< 0.8, < 1. 0, < 0.7	< 1.3, < 2.3, < 1.6

POULTRY

		Residues (ppm)		
Poultry		Feeding level		
Matrix	Analyte	2 ppm	6 ppm	20 ppm
Egg	Combined residues*	N/A	N/A	< 0.1
Fat	Combined residues*	N/A	N/A	< 0.1
Muscle	Combined residues*	N/A	N/A	< 0.1
Liver	Combined residues*	N/A	< 0.1	0.2
Skin	Combined residues*	N/A	N/A	< 0.1

* Combined residues = Combined residues of tebuconazole and hydroxy tebuconazole HWG2061
N/A = Not analyzed due to no measurable residues in the corresponding tissues in the next higher feeding level

Storage Stability

PLANT MATRICES

Freezer storage stability of tebuconazole in/on wheat matrices

Wheat matrix	Demonstrated storage:		Actual maximum storage:	
	Duration (months)	Temperature (°C)	Duration (months)	Temperature (°C)
Grain	63	-20	39	-15 to -20
Straw	63	-20	39.6	-15 to -20
Forage	63	-20	12.6	-15 to -20
Hay	NT	NT	35.7	-15 to -20
Flour	24	-20	5.2	-15
Bran	24	-20	5.2	-15
Shorts	NT	NT	5.3	-15
Middlings	NT	NT	5.3	-15
Germ	NT	NT	5.1	-15
Aspirated grain fraction	NT	NT	2	-15

NT = Not tested. Although there is no data to demonstrate the freezer storage stability of tebuconazole in wheat hay and the processed commodities shorts, middlings, germ and aspirated grain fractions, the behaviour of tebuconazole residues under frozen storage in these matrices should be similar to those reported for grain, straw and forage; the processed commodities of flour and bran under similar frozen storage conditions.

ANIMAL MATRICES

Freezer Storage Stability of Tebuconazole

Animal matrix		Demonstrated storage		Actual maximum storage	
		Duration (months)	Temperature (°C)	Duration (months)	Temperature (°C)
Tebuconazole					
Bovine	Milk	12	-20	5.5	-24
	Liver	5.5	-24	5.5	-24
	Kidney	5.5	-24	5.5	-24
	Muscle	5.5	-24	5.5	-24
	Fat	5.5	-24	5.5	-24
Poultry	Egg	12	-20	5.3	-24
	Liver	6	-10	5.3	-24
	Kidney	6	-10	NT	NT

	Muscle	12	-10	5.3	-24
	Fat	12	-10	5.3	-24
	Skin	5.3	-24	5.3	-24
Hydroxy tebuconazole					
Bovine	Milk	12	-20	5.5	-24
	Liver	5.5	-24	5.5	-24
	Kidney	5.5	-24	5.5	-24
	Muscle	5.5	-24	5.5	-24
	Fat	5.5	-24	5.5	-24
Poultry	Egg	12	-20	5.3	-24
	Liver	6	-10	5.3	-24
	Kidney	6	-10	NT	NT
	Muscle	12	-10	5.3	-24
	Fat	12	-10	5.3	-24
	Skin	5.3	-24	5.3	-24
NT = Not tested. This tissue type was not collected for testing in the poultry feeding study.					

Table 2 Overview of Metabolism Studies and Risk Assessment

Plant Studies	
ROC for enforcement and risk assessment **Wheat**	**Tebuconazole** **((±)-α-[2-(4-chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol)**
Rotational crops	**Tebuconazole** **((±)-α-[2-(4-chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol)**
Metabolic profile in wheat	Tebuconazole is the major metabolite (56 to 99% TRRs) observed in wheat foliage indicating little or no metabolism of tebuconazole occurring in the foliage of the plant. In contrast, wheat grain contains small amount of tebuconazole (6% TRRs), indicating extensive metabolism of the parent occurs. The major metabolic products in the grain, harvested 50 days after the application of tebuconazole, are triazolylalanine (80% TRRs) and triazolylacetic acid (13% TRRs), demonstrating that cleavage of the parent molecule occurs resulting in the liberation of the triazole ring with further modification to form triazolylalanine and triazolylacetic acid. Triazolylalanine is the major residue (80% TRRs) found in the grain. It should be noted that triazolylalanine, which is derived from the triazole ring resulting from cleavage of the parent molecule, is not specific to tebuconazole and is common to fungicides belonging to the triazole family; the compound is separately regulated in Canada with an MRL of 2 ppm.
Animal Studies	
ROC for enforcement and risk assessment	**Tebuconazole** **((±)-α-[2-(4-chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol)** **Hydroxy Tebuconazole (HWG 2061)** **(5-(4-chlorophenyl)-2,2-dimethyl-3-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-pentanediol)**
Metabolic profile in animals	The overall metabolic pathway of tebuconazole in goat and hen is similar. The metabolic pathway proceeds via oxidation of tebuconazole in the t-butyl group to form hydroxy tebuconazole, which is followed either by conjugation (with glucuronic acid or sulfate) or by further oxidation (hen) to form HWG 2443. Conjugation of HWG 2443 with glucuronic acid to form tebuconazole acid glucuronide is observed in the hen. Cleavage of tebuconazole to free-form triazole is noted, but this only constitutes a minor pathway. A similar metabolic pathway is also noted in the rat, i.e., oxidation of tebuconazole to hydroxy tebuconazole followed either by conjugation (with glucuronic acid or sulfate) or by further oxidation to HWG 2443. This is the major metabolic pathway observed in the rats. Cleavage of tebuconazole to free-form triazole is also observed, but it is only a minor pathway.

Fat-soluble residue	Tebuconazole, Hydroxy tebuconazole glucuronide (ECW 4393 2/2)

DIETARY RISK from Food and Water			
Chronic non-cancer dietary risk **ADI = 0.003 mg/kg bw** **EEC (level 2) = 0.0018 ppm**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Food (refined)	**Food + EEC (refined)**
	All infants < 1 year old	**2.5**	**6.6**
	Children 1–2 years	**4.9**	**6.8**
	Children 3–5 years	**3.9**	**5.7**
	Children 6–12 years	**2.3**	**3.5**
	Youth 13–19 years	**1.1**	**2**
	Adults 20–49 years	**1.4**	**2.5**
	Adults 50+ years	**1.5**	**2.7**
	Females 13–49 years	**1.3**	**2.5**
	Total population	**1.7**	**3**
Acute dietary exposure analysis (95th percentile) **ARfD = 0.003 mg/kg bw** **EEC (level 2) = 0.0018 ppm**	**POPULATION**	**ESTIMATED RISK (% of ARfD)**	
	Female 13+	**Food (refined)**	**Food + EEC (refined)**
	Pregnant/not nursing	**4.85**	**6.15**
	Nursing	**6.66**	**7.84**
Cancer risk assessment **Q^{1*} = 0.00589 (mg/kg bw/day)$^{-1}$** **EEC (level 2) = 0.0018 ppm**	**POPULATION**	**ESTIMATED RISK**	
		Food (refined)	**Food + EEC (refined)**
	All infants < 1 year old	4.39×10^{-7}	1.17×10^{-6}
	Children 1–2 years	8.67×10^{-7}	1.20×10^{-6}
	Children 3–5 years	6.92×10^{-7}	1.00×10^{-6}
	Children 6–12 years	4.02×10^{-7}	6.17×10^{-7}
	Youth 13–19 years	1.95×10^{-7}	3.57×10^{-7}
	Adults 20–49 years	2.41×10^{-7}	4.50×10^{-7}
	Adults 50+ years	2.58×10^{-7}	4.77×10^{-7}
	Females 13–49 years	2.31×10^{-7}	4.38×10^{-7}
	Total population	3.01×10^{-7}	5.25×10^{-7}

Appendix IV Environmental Assessment

Table 1 Physical and Chemical Properties of the Active Ingredient Relevant to the Environment

Property	Value	Comments
Water solubility	36 mg/L at 20°C	Soluble in water, potential for leaching and runoff
Vapour pressure	1.3×10^{-6} Pa; 1.275×10^{-8} mm Hg	Non-volatile
Henry's law constant	1.434×10^{-10} atm•m^3/mol	Not volatile from water and moist surfaces
Log K_{ow}	3.7	Potential for bioconcentration/bioaccumulation
pK_a	Does not dissociate	No dissociable functionality
UV–visible absorption	λmax at 220 and no absorbance at λ > 300 nm	Low potential for phototransformation

Table 2 Fate and Behaviour in the Terrestrial Environment

Property	Test Substance	Value	Comments
Abiotic Transformation			
Hydrolysis	Tebuconazole	Stable at pH 5, 7, 9	Not a route of transformation in the environment
Phototransformation on soil	Tebuconazole	DT_{50} = 191 d	Not a significant route of transformation in the environment.
Phototransformation in water	Tebuconazole	DT_{50} = 590 d	Not a significant route of transformation in the environment.
Biotransformation			
Biotransformation in aerobic soil	Tebuconazole	DT_{50} = 770 d	Persistent in soil[a]
Biotransformation in anaerobic soil	Tebuconazole	> 1 year (based on the aerobic soil, aerobic water, and anaerobic water results)	Persistent in soil[a]
Biotransformation in aerobic water	Tebuconazole	DT_{50} =1386 d	Persistent in aerobic water[b]
Biotransformation in anaerobic water	Tebuconazole	DT_{50} = 866 d	Persistent in anaerobic water[b]

Property	Test Substance	Value	Comments
Mobility			
Adsorption/desorption in soil	Tebuconazole	$K_{oc\text{-}ads}$ = 462–1251	Low to moderate mobility
	Triazole (transformation Product)	$K_{oc\text{-}ads}$ = 21.1–126.7	Very high to high mobility
Soil leaching (TLC)	Tebuconazole	Rf values of 0.09–0.22	Low potential for mobility in soil
Soil leaching (aged soil column)	Tebuconazole	Less than 1% of the radioactivity leached through the column (44.5 cm in length), and most of the recovered radioactivity identified as tebuconazole. Other extracted radiolabelled compounds were reported to be less than 10% of the total recovery radioactivity.	Low potential for mobility in soil
Field Studies			
Canadian field dissipation			Multiyear field study being conducted

[a] According to the classification of Goring et al. (1975)

[b] According to the classification scheme of McEwen and Stephenson (1979)

Table 3 Fate and Behaviour in the Aquatic Environment

Property	Test Material	Value	Comments
Abiotic Transformation			
Hydrolysis	Tebuconazole	stable to hydrolysis at pH 5, 7, 9	Not a route of transformation in the environment
Phototransformation in water	Tebuconazole	DT_{50} 590 d	Not a route of transformation in the environment
Biotransformation			
Biotransformation in aerobic/anaerobic water systems	Tebuconazole	aerobic DT_{50} = 1386 d anaerobic DT_{50} = 866 d	Tebuconazole rapidly partitions to sediments, where it persists Persistent in aerobic water/sediment systems No major transformation products

Table 4 Major Groundwater and Surface Water Model Inputs for Level 1 Assessment of Tebuconazole

Type of input	Parameter	Value
Application information	Crop(s) to be treated	Wheat
	Maximum allowable application rate per year (kg a.i./ha)	0.126
	Maximum rate each application (kg a.i./ha)	0.126
	Maximum number of applications per year	1
	Minimum interval between applications (days)	Not applicable
	Method of application	Ground spayer or aerial application
Environmental fate characteristics	Hydrolysis half-life at pH 7 (days)	Stable
	Photolysis half-life in water (days)	590
	Adsorption K_{oc} (mL/g)	462 (smallest value)
	Aerobic soil biotransformation half-life (days)	Stable
	Aerobic aquatic biotransformation half-life (days)	Stable
	Anaerobic aquatic biotransformation half-life (days)	866

Table 5 Level 1 Estimated Environmental Concentrations of Tebuconazole in Potential Drinking Water Sources

Groundwater (µg a.i./L)		Surface Water (µg a.i./L)			
		Reservoir		Dugout	
Acute[1]	Chronic[2]	Acute[3]	Chronic[4]	Acute[3]	Chronic[4]
40.2	40.1	6.6	2	154.8	153

[1] 90th percentile of daily average concentrations

[2] 90th percentile of yearly average concentrations

[3] 90th percentile of yearly peak concentrations

[4] 90th percentile of yearly average concentrations

Table 6 Major Groundwater and Surface Water Model Inputs for Level 2 Assessment of Tebuconazole

Type of input	Parameter	Value
Application information	Crop(s) to be treated	Wheat
	Maximum allowable application rate per year (kg a.i./ha)	0.126
	Maximum rate each application (kg a.i./ha)	0.126
	Maximum number of applications per year	1
	Minimum interval between applications (days)	Not applicable

Type of input	Parameter	Value
	Method of application	Ground spayer or aerial application
Environmental fate characteristics	Hydrolysis half-life at pH 7 (days)	Stable
	Photolysis half-life in water (days)	590
	Adsorption K_{oc} (mL/g)	936 (mean of 6 values)
	Aerobic soil biotransformation half-life (days)	770 (calculated)
	Aerobic aquatic biotransformation half-life (days)	1386 (calculated)
	Anaerobic aquatic biotransformation half-life (days)	866

Table 7 Level 2 Estimated Environmental Concentrations of Tebuconazole in Potential Drinking Water Sources

Groundwater (µg a.i./L)		Surface water (µg a.i./L)			
		Reservoir		Dugout	
Acute[1]	Chronic[2]	Acute[3]	Chronic[4]	Acute[3]	Chronic[4]
9.1	9.1	NC	NC	24.5	23.3

[1] 90th percentile of daily average concentrations

[2] 90th percentile of yearly average concentrations

[3] 90th percentile of yearly peak concentrations

[4] 90th percentile of yearly average concentrations

NC Level 2 EECs were not calculated for the reservoir scenario, as the Level 1 reservoir EECs were smaller than the dugout EECs.

Table 8 Updated Level 2 Estimated Environmental Concentrations of Tebuconazole in Drinking Water (wheat 126 g a.i./ha)

	Surface Water (µg a.i./L)[1]			
	Reservoir		Dugout	
Scenario	Acute[2]	Chronic[3]	Acute[2]	Chronic[3]
MB–every year	3.05	2.12	24.5	23.3
MB–skip every third year	2.16	1.51	16.96	16.09
MB–alternate years	1.69	1.14	12.86	12.25
MB–every third year	1.29	0.82	8.40	7.89
ON–every year	1.49	1.11	N/A[4]	
ON–skip every third year	1.18	0.88		
ON–alternate years	1.12	0.58		
ON–every third year	0.95	0.48		
QC–every year	3.83	2.08	N/A[4]	
QC–skip every third year	3.56	1.80		
QC–alternate years	3.08	1.23		
QC–every third year	2.88	1.07		
SK–every year	4.21	2.46	10.03	9.54
SK–skip every third year	1.88	1.65	6.51	6.29
SK–alternate years	1.32	1.03	4.97	4.74
SK–every third year	1.06	0.74	3.58	3.39

1 Reported levels are from application date that produced the highest EECs

2 90th percentile of yearly peaks

3 90th percentile of yearly averages

4 Dugout not relevant to this geographical scenario

MB = Manitoba; ON = Ontario; QC = Quebec; SK = Saskatchewan

Table 9 Maximum EEC in Vegetation and Insects after a Direct Overspray

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/Dry Weight Ratios	EEC (mg a.i./kg dw)
Short range grass	27	3.3[b]	89
Leaves and leafy crops	14	11[b]	155
Long grass	12	4.4[b]	54
Forage crops	15	5.4[b]	82
Small insects	7	3.8[c]	25
Pods with seeds	1	3.9[c]	5
Large insects	1	3.8[c]	4
Grain and seeds	1	3.8[c]	4
Fruit	1.7	7.6[c]	13

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994)

[b] Fresh / dry weight ratios from Harris (1975)

[c] Fresh / dry weight ratios from Spector (1956)

Table 10 Maximum EEC in Diets of Birds and Mammals

Organism	Matrix	EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	22.06
Mallard duck	30% large insects 70% grain	4.26
Rat	70% short grass 20% grain/seeds 10% large insects	63.57
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	63.18
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	95.05

Table 11 Effects on Terrestrial Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Invertebrates				
Earthworm	Acute	Tebuconazole	LC_{50} =1381 mg a.i./kg soil NOEC = 178 mg a.i./kg soil	N/A
Bee	Oral	Tebuconazole	NOEC = 0.6 µg a.i./bee[b]	N/A
	Contact	Tebuconazole	LD_{50} = 176 µg a.i./bee	Relatively non-toxic
Birds				
Bobwhite quail	Acute oral	Tebuconazole	LD_{50} > 1200 mg/kg for the bobwhite males, 1555 mg/kg for the bobwhite ♀ NOEC = 432 mg/kg bw	Slightly toxic
	Dietary	Tebuconazole	LC_{50} > 5000 mg a.i./kg diet	Practically non-toxic
Mallard duck	Acute			No data
	Dietary	Tebuconazole	LC_{50} > 4816 mg a.i./kg NOEC < 4816 mg a.i./kg	Slightly toxic
	Reproduction	Tebuconazole	NOEC = 75.8 mg/kg	N/A
Mammals				
Rat	Acute oral	Tebuconazole	LD_{50} = 2850 mg/kg bw	Practically non-toxic
	Reproduction	Tebuconazole	NOEC = 18.4 mg/kg	N/A
		Formulation (Folicur 432F Foliar Fungicide)	LD_{50} = 3743 mg/kg bw	Practically non-toxic
	Acute dermal	Tebuconazole	LD_{50} > 5000 mg/kg bw	Low dermal toxicity
		Formulation (Folicur 3.6 F)	LD_{50} > 2011 mg/kg bw	Low dermal toxicity
	Acute inhalation	Tebuconazole	LC_{50} aerosol > 0.371 mg/L LC_{50} dust > 5.093 mg/L	Low acute toxicity
		Formulation (Folicur 432F Foliar Fungicide)	LC_{50} > 2.51 mg/L	Low acute toxicity

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
	Acute neurotoxicity	Tebuconazole	**Neurotoxicity:** NOEL = 100 mg/kg bw	N/A
	Short-term (3 weeks to 3 months) dietary	Tebuconazole	NOEL = 30 mg/kg bw/day (3-week rat study) NOEL = 7.5 and 9.4 mg/kg bw/day, M/F (3-month rat study)	N/A
	Short-term inhalation	Tebuconazole	NOEL = 0.156 mg/L/d	N/A
	Subchronic neurotoxicity	Tebuconazole	**Systemic toxicity:** NOEL = 400 ppm (29.1 and 34 mg/kg bw/d for M and F, respectively) **Neurotoxicity:** NOEL = 1600 ppm (107 and 122 mg/kg bw/d for M and F, respectively)	No treatment related effects observed
	Chronic (2-year dietary)	Tebuconazole	NOEL = 100 ppm (4.7, and 6.5 mg/kg bw/d for M and F, respectively)	N/A
	Reproduction	Tebuconazole	NOEL = 300 ppm (24.4 and 30.9 mg/kg bw/d for M and F, respectively)	N/A
	Developmental neurotoxicity	Tebuconazole	**Systemic toxicity:** NOEL = 300 ppm (22 mg/kg bw/d) **Developmental toxicity:** NOEL = 300 ppm (22 mg/kg bw/d) **Neurotoxicity:** NOEL = 1000 ppm (65 mg/kg bw/d)	No treatment related neurotoxic effects observed
Mouse	Acute oral	Tebuconazole	LD_{50} = 4000 mg/kg bw	Practically non-toxic
	Chronic (21-month dietary)	Tebuconazole	NOEL= 60 ppm (18.2 and 26.1 mg/kg bw/d for M and F, respectively)	N/A
	Reproduction, dietary	Tebuconazole	**Maternal systemic effects:** NOEL = 10 mg/kg bw/d **Developmental effects:** NOEL = 3 mg/kg bw/d	Indicative of teratogenic potential and ↑ fetal sensitivity

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Rabbit	Short-term (3 weeks) dermal	Tebuconazole	NOEL = 1000 mg/kg bw/d	No adverse treatment related findings
	Reproduction	Tebuconazole	**Maternal systemic effects:** NOEL = 30 mg/kg bw/d **Developmental effects:** NOEL = 10 mg/kg bw/d	Indicative of teratogenic potential and ↑ fetal sensitivity
Vascular Plants				
Vascular plant	Seedling emergence (tier 2)	Folicur 432F Foliar Fungicide	NOEC = 57 (shoot height of tomato) EC$_{25}$ = 102 g a.i./ha (weight of tomato)	Study was considered supplemental
	Vegetative vigour (tier 1)	Folicur 432F Foliar Fungicide	NOEC = 453 g a.i./ha[b] EC$_{25}$ > 453 g a.i./ha	No adverse effects were observed in the vegetative vigour test for all crops tested. Study was considered supplemental

[a] Atkins et al. (1981) for bees and USEPA classification for others, where applicable

[b] No effects were observed at the highest dose tested

Table 12 Effects on Aquatic Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Freshwater Species				
Daphnia magna	Acute	Tebuconazole	NOEC = 0.74 mg a.i./L	N/A
	Chronic	Tebuconazole	EC$_{50}$ = 0.33 mg a.i./L NOEC = 0.12 mg a.i./L	N/A
Rainbow trout (*Oncorhynchus mykiss*)	Acute	Tebuconazole	LC$_{50}$ = 4.4 mg a.i./L NOEC = 1.5 mg a.i./L	Moderately toxic
	Chronic (early life stage)	Tebuconazole	NOEC = 12 µg a.i./L	N/A
Bluegill sunfish (*Lepomis macrochirus*)	Acute	Tebuconazole	LC$_{50}$ = 5.7 mg a.i./L NOEC <1.4 mg a.i./L	Moderately toxic

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Freshwater green algae (*Scenedesmus subspicatus*)	Acute	Tebuconazole	EC_{50} for biomass 1.64 mg a.i./L EC_{50} for growth rate 4.01 mg a.i./L NOEC for biomass 0.32 mg a.i./L NOEC for growth rate 1.0 mg a.i./L	N/A
Freshwater green algae (*Selenastrum capricornutum*)	Acute	Tebuconazole	NOEC =2.46 mg a.i./L EC_{25} = 1.96 mg a.i./L EC_{50} = 2.83 mg a.i./L	N/A
Vascular plant *Lemna gibba* G3	Dissolved	Tebuconazole	Based on frond No: NOEC = 62.3 µg a.i./L EC_{25} = 91.2 µg a.i./L EC_{50} = 144.4 µg a.i./L; Based on biomass: NOEC = 62.3 µg a.i./L EC_{25} = 96.7 µg a.i./L EC_{50} = 179.8 µg a.i./L	N/A
Marine Species				
Crustacean (mysid shrimp) (*Mysidopsis bahia*)	Acute	Tebuconazole	LC_{50} = 0.45 mg a.i./L NOEC < 0.30 mg a.i./L	Highly toxic
Mollusk (Eastern oyster) *Crassostrea virginica*)	Acute	Tebuconazole	LC_{50} = 3.0 mg a.i./L NOEC 1.7 mg a.i./L	Moderately toxic
Sheepshead minnow (*Cyprinodon variegatus*)	Chronic	Tebuconazole	The NOECs$_{\text{Fo generation}}$, based on adverse effects on length and reproduction = 43.6 and 96.7 µg a.i./L, respectively $LC_{50\ \text{F1 generation}}$ > 97.8 µg a.i./L NOECs$_{\text{F1 generation}}$, based on mortality and adverse effects on hatching success = 97.8 and 97.8 µg a.i./L	N/A

[a] USEPA classification, where applicable

Table 13 Environmental Risk Classification Scheme

Risk Quotient	Degree of Risk
< 0.1	Negligible
≥ 0.1–1	Low
≥ 1–10	Moderate
≥ 10–100	High
≥ 100–1000	Very high
≥ 1000	Extremely high

Table 14 Risk to Terrestrial Organisms

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Invertebrates					
Earthworm	Acute	NOEC = 178mg a.i./kg soil	0.056 mg a.i./kg soil	0.000315	Negligible
Bee	Contact	LD_{50} = 176 µg a.i./bee equivalent to 197.12 kg a.i./ha	0.126 kg/ha	0.00063	Negligible
Birds					
Bobwhite quail	Acute oral	NOEC = 432 mg a.i./kg	22.06 mg a.i./kg dw diet	219 days of intake to reach to NOEL	Negligible
	Dietary	NOEC < 325 mg a.i./kg diet	22.06 mg a.i./kg dw diet	0.0679	Negligible
	Reproduction	NOEC = 18.4 mg a.i./kg diet	22.06 mg a.i./kg dw diet	1.2	Moderate
Mallard duck	Dietary	NOEC > 4816 mg a.i./kg feed	4.26 mg a.i./kg dw diet	0.000885	Negligible
	Reproduction	NOEC = 75.8 mg a.i./kg diet	4.26 mg a.i./kg dw diet	0.0562	Negligible

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Mammals					
Rat	Acute oral	LD_{50} = 2850 mg/kg bw NOEL= 1/10 LD_{50} = 285 mg/kg bw	63.57 mg/kg dw diet	26.2 days of intake to reach to NOEL	Negligible
	Acute neurotoxicity	NOEL = 100 mg/kg bw	63.57 mg/kg dw diet	9.2 days of intake to reach to NOEL	Negligible
	Short-term dietary	NOEL = 7.5 mg/kg bw/d	63.57 mg/kg dw diet	8.5	Moderate
Mouse	Acute oral	LD_{50} = 4000 mg/kg bw NOEL= 1/10 LD_{50} = 400 mg/kg bw	63.18 mg/kg dw diet	35 days of intake to reach to NOEL	Negligible
	Reproduction	NOEL = 3 mg/kg bw	63.18 mg/kg dw diet	21.1	High
Vascular plants					
Terrestrial plants	Seedling emergence	EC_{25} = 102 g a.i./ha	126 g a.i./ha	1.2	Moderate
	Vegetative vigour	NOEC > 453 g a.i./ha	126 g a.i./ha	No toxic effects	Negligible

Table 15 Risk to Aquatic Organisms

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Freshwater Species					
Daphnia magna	Acute	NOEC = 0.74 mg/L	0.042 mg a.i./L	0.057	Negligible
	Chronic	NOEC = 0.12 mg/L	0.042 mg a.i./L	0.35	Low
Rainbow trout	Acute	NOEC = 1.5 mg/L	0.042 mg a.i./L	0.028	Negligible
	Chronic	NOEC = 0.012 mg/L	0.042 mg a.i./L	3.5	Moderate
Bluegill sunfish	Acute	NOEC = 1.4 mg/L	0.042 mg a.i./L	0.03	Negligible

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Freshwater alga (*Scenedesmus subspicatus*)	Acute	**Biomass:** NOEC = 0.32 mg/L	0.042 mg a.i./L	0.131	Low
		Growth rate: NOEC = 1 mg/L	0.042 mg a.i./L	0.042	Negligible
Freshwater alga (*Selenastrum capricornutum*)	Acute	**Cell density:** NOEC = 2.46 mg/L	0.042 mg a.i./L	0.017	Negligible
Vascular plant (*Lemna gibba*)	Acute	**Frond no.:** NOEC = 0.0623 mg/L	0.042 mg a.i./L	0.674	Low
	Acute	**Biomass:** NOEC = 0.0623 mg/L	0.042 mg a.i./L	0.674	Low
Marine Species					
Crustacean (mysid shrimp)	Acute	NOEC = 0.3 mg/L	0.042 mg a.i./L	0.14	Low
Mollusk (Eastern oyster)	Acute	NOEC = 1.7 mg/L	0.042 mg a.i./L	0.025	Negligible
Sheepshead	Chronic (life cycle)	NOEC = 0.0436 mg/L	0.042 mg a.i./L	0.963	Low

Table 16 Methods for Environmental Residue Analysis

Matrix	Method ID	Analyte	Method	Spike Level (mg/kg)	Mean % Recovery ± SD	LOQ (mg/kg)
Soil	Report # 107704	Tebuconazole	Electrospray HPLC/MS-MS	0.01	99.5 ± 4.2 (*n* = 5)	0.01
					95.5 ± 1.1 (*n* = 5)	
Turf	Report # 107704	Tebuconazole	Electrospray HPLC-MS/MS	0.01	106.9 ± 2.8 (*n* = 5)	0.01
				0.10	94.8 ± 1.0 (*n* = 5)	

Matrix	Method ID	Analyte	Method	Spike Level (mg/kg)	Mean % Recovery ± SD	LOQ (mg/kg)
Sediment	Report # 103802	Tebuconazole	GC (nitrogen-phosphorus detector) GC-NPD	0.05 0.10 0.20 0.50 1.0	75.0 ($n = 3$) 112.5 ($n = 1$) 104.1 ($n = 4$) 95.6 ($n = 4$) 96.0 ($n = 1$)	0.05
Water	Report # 94295 and 101341	Tebuconazole	Gas chromatography / TSD (nitrogen-phosphorous)	0.005	94–102	0.005 (lowest concentration detected)
Biota (plant matrix): Wheat/barley /oat and rye, peanuts, bananas and grapes	Report #s 94295	Tebuconazole	GC-TSD (nitrogen-phosphorous)	0.05–5.0	90–103	0.05 (lowest determined concentration)
Wheat/barley and oats	101341		GC-NPD	Not reported in the review	Not reported in the review	10.1–0.02
Animal matrix: Juvenile* bluegill sunfish	Report #s 98037*	Tebuconazole	HPLC and mass spectral analysis (MS/GS)			Not provided.*
Bovine and poultry tissue	101316		GC and GC-MS	Not reported in the review	Not reported in the review	0.1

* This method was not acceptable because C^{14} was used and the initial spiking levels were not reported (the fish tissues were from a bioconcentration study, the initial spiking levels were not reported)

References

Atkins E.L., D. Kellum and K.W. Atkins. 1981. *Reducing Pesticide Hazards to Honey Bees: Mortality Prediction Techniques and Integrated Management Techniques*. University of California, Division of Agricultural Sciences, Leaflet 2883. 23 p.

Bailey, K.L., et al. 2003. *Disease of Field Crops in Canada*. The Canadian Phytopathological Society. 304 p.

Dilantha Fernando, W.G. 2001. Biological Control of Fusarium Head Blight of Wheat and Barley. In: Proc. Second Canadian Workshop on Fusarium Head Blight, 3–5 November 2001. Ottawa, Ontario.

Dilantha Fernando, W.G. 2003. Biological Control Methods to Manage Fusarium Head Blight Disease of Wheat: Is it a Short or Long Term Solution to the Problem? In: Proc. Third Canadian Workshop on Fusarium Head Blight, 9–12 December 2003. p 106.

European and Mediterranean Plant Protection Organization. 1997. *Guidelines for the Efficacy Evaluation of Plant Protection Products, Volume 2, Fungicides and Bactericides*. pp. 34–37, 41–44.

Fletcher, J.S., J.E. Nellessen and T.G. Pfleeger. 1994. Literature Review and Evaluation of the EPA Food-Chain (Kenaga) Nomogram, an Instrument for Estimating Pesticide Residues on Plants. *Environmental Toxicology and Chemistry*. 13:1383–1391.

Goring C.A.I., D.A Laskwoski, J.H. Hamaker and R.W. Meikle. 1975. Principles of Pesticide Degradation In Soil. In: R. Haque and V.H. Freed, ed., *Environmental Dynamics of Pesticides*. Plenum Press, New York, New York, USA. pp. 135–172.

Harris, L. E. 1975. *Guide for Estimating Toxic Residues in Animal Feeds or Diets*. EPA/540/9-75-019 (NTIS reference #: PB 243 748). USEPA, Washington, D.C.

Hoerger F., and E.E. Kenaga. 1972. Pesticide Residues on Plants: Correlation of Representative Data as Basis For Estimation of Their Magnitude in the Environment. In: F. Coulston and F. Korte, ed., *Environmental Quality and Safety—Global Aspects of Chemistry, Toxicology and Technology as Applied to the Environment*, Vol. I. Thieme, Stutgart, and Academic Press, New York. pp. 9–28.

Kenaga E.E. 1973. Factors to Be Considered in the Evaluation of the Toxicity of Pesticides to Birds in Their Environment. In: F. Coulston and F. Korte, ed., *Environmental Quality and Safety—Global Aspects Of Chemistry, Toxicology and Technology as Applied to the Environment*, Volume II. Thieme, Stuttgart, and Academic Press, New York. pp. 166–181.

Manitoba Agriculture, Food and Rural Initiatives. 2003. Pest Management - Plant Disease, 2001: Dealing with Fusarium Head Blight.

McCall, J.P., D.A. Laskowski, R.L. Swann and J.J. Dishburger. 1981. Measurement of Sorption Coefficients of Organic Chemicals and Their Use in Environmental Fate Analysis. In *Test Protocols for Environmental Fate and Movement of Toxicants*. Proceedings of a symposium. Association of Official Analytical Chemists, 94th Annual Meeting, 21–22 October 1980. Washington, District of Columbia. pp. 89–109.

McEwen F.L., and G.R. Stephenson. 1979. *The Use and Significance of Pesticides in the Environment*. John Wiley and Sons Inc. Toronto. 282 p.

Miller, W.E., J.C. Green and T. Shiroyama. 1978. The *Selenastrum capricornutum* Printz Algal Assay Bottle Test. EPA-600/9-78-018. United States Environmental Protection Agency, Washington, District of Columbia. pp. 17–18.

Schisler, D.A. 2003. Greenhouse and Field Evaluation of Biological Control of Fusarium Head Blight on Durham Wheat. *Plant Disease*. 86:1350–1356.

Spector, W.S. 1956. *Handbook of Biological Data*. W.B. Saunders, Philadelphia, Pennsylvania. p. 78, 187.

Tenuta, A. 2003. Integrated Fusarium Head Blight Management: Employing all the Tools. In: R.Clear, ed. Third Canadian Workshop on Fusarium Head Blight, 9–12 December 2003. pp. 114–115. Available at http://grainscanada.gc.ca/Cdngrain/fusarium/workshop/2003/3rdCWFHB-2003.pdf. Accessed 20 October 2006.

Urban D.J., and N.J. Cook. 1986. *Hazard Evaluation Division, Standard Evaluation Procedure: Ecological Risk Assessment*. United States Environmental Protection Agency, EPA 540/9-85-001, Washington, DC. 96 p.

United States Environmental Protection Agency. 1985a. *Hazard Evaluation Division, Standard Evaluation Procedure: Avian Single-Dose Oral LD_{50}*. Document code EPA-540/9-85-001. Office of Pesticides Programs, Washington, District of Columbia.

United States Environmental Protection Agency. 1985b. *Hazard Evaluation Division, Standard Evaluation Procedure: Avian Dietary LC_{50} Test*. Document code EPA-540/9-85-008. Office of Pesticides Programs, Washington, District of Columbia.

United States Environmental Protection Agency. 1985c. *Hazard Evaluation Division, Standard Evaluation Procedure: Wild Mammal Toxicity Test*. Document code EPA-540/9-85-004. Office of Pesticides Programs, Washington, District of Columbia.

United States Environmental Protection Agency. 1985d. *Hazard Evaluation Division, Standard Evaluation Procedure: Acute Toxicity Test for Freshwater Fish*. Document code EPA-540/9-85-006. Office of Pesticides Programs, Washington, District of Columbia.

United States Environmental Protection Agency. 1985e. *Hazard Evaluation Division, Standard Evaluation Procedure: Acute Toxicity Test for Estuarine and Marine Organisms (shrimp 96-hour acute toxicity test).* Document code EPA-540/9-85-010. Office of Pesticides Programs, Washington, District of Columbia.

United States Environmental Protection Agency. 1985f. *Hazard Evaluation Division, Standard Evaluation Procedure: Acute Toxicity Test for Estuarine and Marine Organisms (mollusc 96-hour flow-through shell deposition study).* Document code EPA-540/9-85-011. Office of Pesticides Programs, Washington, District of Columbia.

United States Environmental Protection Agency. 1994. *Pesticide Reregistration Rejection Rate Analysis: Ecological Effects.* Document code EPA 738-R-94-035. Office of Pesticides Programs, Washington, District of Columbia.

United States Environmental Protection Agency. 1988. *Recommendations for and Documentation of Biological Values for Use in Risk Assessment.* PB 179874, Document code EPA 600/6-87/008. Cincinnati, Ohio.

United States Environmental Protection Agency. 1996a. *Background—Nontarget Plant Testing.* Ecological Effects Test Guidelines, OPPTS 850.4000. Document code EPA 712-C-96-151. Washington, District of Columbia.

United States Environmental Protection Agency. 1996b. *Seedling Emergence, Tier II.* Ecological Effects Test Guidelines, OPPTS 850.4225. Document code 172-C-96-363. Washington, District of Columbia.

United States Environmental Protection Agency. 1999a. *Bacillus subtilis* GBO3 (129068). USEPA Fact Sheet. Available at: www.epa.gov/pesticides/biopesticides/ingredients/factsheets/factsheet_129068.htm. Accessed on 20 October 2006.

United States Environmental Protection Agency. 1999b. *Bacillus subtilis* MBI 600 (129082). USEPA Fact Sheet. Available at: www.epa.gov/pesticides/biopesticides/ingredients/factsheets/factsheet_129082.htm. Accessed on 20 October 2006.

United States Food and Drug Administration. 1993. *Pesticide Analytical Manual* (PAM), Volume I: Multiresidue Methods, Third Edition. Available through the National Technical Information Service, Springfield, Virginia.